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(54) **Title: ANTI-INFLAMMATORY AGENTS**

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(57) Abstract

Compounds of formula (I) wherein R¿4 is an ester or thioester group, and R, R¿1, R¿2 and R¿3 are as defined in the specification, inhibit intracellular leukotriene-A¿4 hydrolase activity and have anti-inflammatory activity.

(57) Abrégé

Cette invention concerne des composés représentés par la formule (I) dans laquelle R¿4 est un ester ou un groupe thioester, et R, R¿1, R¿2 et R¿3 sont conformes à la spécification du descriptif. Ces composés inhibent l'activité hydrolase leukotriène-A¿4 intracellulaire et ont une action anti-inflammatoire.

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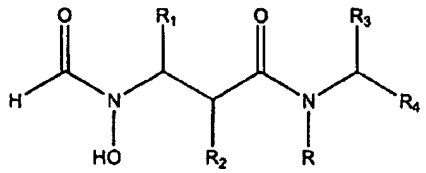

(I)

(57) Abstract

Compounds of formula (I) wherein R_4 is an ester or thioester group, and R, R_1, R_2 and R_3 are as defined in the specification, inhibit intracellular leukotriene-A_4 hydrolase activity and have anti-inflammatory activity.

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Description

Anti-Inflammatory Agents

The present invention relates to the use of certain esters and thioesters for the treatment of diseases responsive to inhibition of intracellular leukotriene-A_4 hydrolase activity.

Background to the Invention

The leukotriene cascade of arachadonic acid is a key mechanism in many inflammatory and allergic disease states. The dihydroxy fatty acid leukotriene B_4 (LTB_4), produced by this cascade, is a key pro-inflammatory mediator. LTB_4 stimulates adhesion of circulating neutrophils to vascular endothelium, directs their migration toward sites of inflammation, and induces secretion of further inflammatory mediators. (For reviews see R.A. Lewis et al, N. Engl. J. Med. 1990, 323, 645-655 and M. -Q. Zhang, Curr. Med. Chem. 1997, 4, 67-78.) Leukotriene-A_4 hydrolase (LTA_4-hydrolase) (EC 3.3.2.6) is an enzyme that catalyses the final and rate limiting step in the synthesis of LTB_4. Inhibition of LTA_4 hydrolase selectively blocks the biosynthesis of LTB_4 which may provide an advantage over current inhibitors, such as those of 5-lipoxygenase, that block earlier in the leukotriene cascade and as a result are less selective.

Disease states associated with elevated levels of LTB_4, and which are therefore considered to be responsive to inhibition of intracellular leukotriene-A_4 hydrolase activity include asthma, inflammatory bowel disease, psoriasis and arthritis.

Peptidomimetic compounds, such as bestatin, captopril and kelatorphan exhibit LTA_4 hydrolase inhibitory activity against isolated enzyme (T.D. Penning et al, Biorg. Med. Chem. Lett., 1995, 5, p2517-2522). However, these compounds are unable to effectively penetrate cells and hence have little anti-inflammatory activity. There is therefore a need in the art for compounds which are capable of inhibiting intracellular LTA_4 hydrolase activity.

Brief Description of the Invention

This invention is based on the finding that certain esters and thioesters containing an N-formyl hydroxylamine group are capable of inhibiting intracellular LTA_4 hydrolase activity, resulting in efficient attenuation of LTB_4 biosynthesis. Those esters and thioesters are therefore of use for the treatment of diseases responsive to such inhibiton, for example inflammatory and allergic conditions including asthma, rheumatoid arthritis, osteoarthritis, multiple sclerosis, ulcerative colitis, contact and atopic dermatitis, psoriasis, inflammatory bowel disease and Crohn's disease.

The following patent publications disclose compounds containing an N-formyl hydroxylamine group which are stated to be inhibitors of matrix metalloproteinases (MMPs), and thus potentially of value for the treatment of diseases involving inapproriate degradation of the extracellular matrix. However, few examples of such compounds have been specifically made and described those publications:

EP-B-0236872	(Roche)
WO 92/09563	(Glycomed)
WO 92/04735	(Syntex)
WO 95/19965	(Glycomed)
WO 95/22966	(Sanofi Winthrop)
WO 95/33709	(Roche)
WO 96/23791	(Syntex)
WO 96/16027	(Syntex/Agouron)
WO 97/03783	(British Biotech)
WO 97/18207	(DuPont Merck)

Brief Description of the Invention

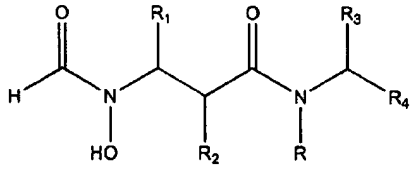
This invention is based on the identification of a class of ester and thioester compounds containing an N-formyl hydroxylamine group, which are capable of inhibiting intracellular LTA_4 hydrolase activity, resulting in efficient attenuation of LTB_4 biosynthesis. Those esters and thioesters are therefore of use for the treatment

of diseases responsive to such inhibiton, for example inflammatory and allergic conditions including asthma, rheumatoid arthritis, osteoarthritis, multiple sclerosis, ulcerative colitis, contact and atopic dermatitis, psoriasis, inflammatory bowel disease and Crohn's disease.

The ester and thioester compounds in question have certain structural similarities to known MMP inhibitors generically disclosed in the foregoing patent publications. Most of those prior art publications are concerned with amides rather than esters or thioesters group, but a a few (WO 92/09563, WO 95/19965 and WO 95/22966) include within their generic disclosure compounds having a carboxylate ester group in place of the amide group. The carboxylate ester compounds with which this invention is concerned thus represent a selection of a notional subclass from the compounds proposed in the art as MMP inhibitors or for other purposes, for a specific and previously unrecognised pharmaceutical utility - inhibiting intracellular LTA_4 hydrolase activity.

Detailed Description of the Invention

In its broadest aspect, the present invention provides a method for treatment of mammals suffering diseases responsive to inhibition of intracellular leukotriene-A_4 hydrolase activity, comprising administering to the mammal suffering such disease an amount of a compound of general formula (I) or a pharmaceutically acceptable salt hydrate or solvate thereof sufficient to inhibit such activity:



(I)

wherein

R is hydrogen or (C_1-C_6)alkyl;

R_1 is hydrogen;

(C_1-C_6)alkyl;

(C_2-C_6)alkenyl;

phenyl or substituted phenyl;

phenyl (C_1-C_6)alkyl or substituted phenyl(C_1-C_6)alkyl;

phenyl (C_2-C_6)alkenyl or substituted phenyl(C_2-C_6)alkenyl

heterocyclyl or substituted heterocyclyl;

heterocyclyl(C_1-C_6)alkyl or substituted heterocyclyl(C_1-C_6)alkyl;

a group BSO_nA- wherein n is 0, 1 or 2 and B is hydrogen or a (C_1-C_6) alkyl, phenyl, substituted phenyl, heterocyclyl substituted heterocyclyl, (C_1-C_6)acyl, phenacyl or substituted phenacyl group, and A represents (C_1-C_6)alkylene;

amino(C_1-C_6)alkyl, (C_1-C_6)alkylamino(C_1-C_6)alkyl, di(C_1-C_6)alkylamino(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, mercapto(C_1-C_6)alkyl or carboxy(C_1-C_6) alkyl wherein the amino-, hydroxy-, mercapto- or carboxyl-group are optionally protected or the carboxyl- group amidated;

lower alkyl substituted by carbamoyl, mono(lower alkyl)carbamoyl, di(lower alkyl)carbamoyl, di(lower alkyl)amino, or carboxy-lower alkanoylamino; or

a cycloalkyl, cycloalkenyl or non-aromatic heterocyclic ring containing up to 3 heteroatoms, any of which may be (i) substituted by one or more substituents selected from C_1-C_6 alkyl, C_2-C_6 alkenyl, halo, cyano (-CN), $-CO_2H$, $-CO_2R$, $-CONH_2$, -CONHR, $-CON(R)_2$, -OH, -OR, oxo-, -SH, -SR, -NHCOR, and $-NHCO_2R$ wherein R is C_1-C_6 alkyl or benzyl and/or (ii) fused to a cycloalkyl or

heterocyclic ring;

R_2 is a C_1-C_{12} alkyl,
C_2-C_{12} alkenyl,
C_2-C_{12} alkynyl,
phenyl(C_1-C_6 alkyl)-,
heteroaryl(C_1-C_6 alkyl)-,
phenyl(C_2-C_6 alkenyl)-,
heteroaryl(C_2-C_6 alkenyl)-,
phenyl(C_2-C_6 alkynyl)-,
heteroaryl(C_2-C_6 alkynyl)-,
cycloalkyl(C_1-C_6 alkyl)-,
cycloalkyl(C_2-C_6 alkenyl)-,
cycloalkyl(C_2-C_6 alkynyl)-,
cycloalkenyl(C_1-C_6 alkyl)-,
cycloalkenyl(C_2-C_6 alkenyl)-,
cycloalkenyl(C_2-C_6 alkynyl)-,
phenyl(C_1-C_6 alkyl)O(C_1-C_6 alkyl)-, or
heteroaryl(C_1-C_6 alkyl)O(C_1-C_6 alkyl)- group,
any one of which may be optionally substituted by
C_1-C_6 alkyl,
C_1-C_6 alkoxy,
halo,
cyano (-CN),
phenyl or heteroaryl, or
phenyl or heteroaryl substituted by
C_1-C_6 alkyl,
C_1-C_6 alkoxy,
halo, or
cyano (-CN);

R_3 is the characterising group of a natural or non-natural α amino acid in which any functional groups may be protected; and

R_4 is an ester or thioester group,

or a pharmaceutically acceptable salt, hydrate or solvate thereof.

In another broad aspect of the invention, there is provided the use of a compound of formula (I) as defined in claim 1 in the preparation of a pharmaceutical or veterinary composition for treatment of mammals suffering diseases responsive to inhibition of intracellular leukotriene-A_4 hydrolase activity.

As used herein the term "(C_1-C_6)alkyl" or "lower alkyl" means a straight or branched chain alkyl moiety having from 1 to 6 carbon atoms, including for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, n-pentyl and n-hexyl.

The term "(C_2-C_6)alkenyl" means a straight or branched chain alkenyl moiety having from 2 to 6 carbon atoms having at least one double bond of either E or Z stereochemistry where applicable. This term would include, for example, vinyl, allyl, 1- and 2-butenyl and 2-methyl-2-propenyl.

The term "C_2-C_6 alkynyl" refers to straight chain or branched chain hydrocarbon groups having from two to six carbon atoms and having in addition one triple bond. This term would include for example, ethynyl, 1-propynyl, 1- and 2-butynyl, 2-methyl-2-propynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl and 5-hexynyl.

The term "cycloalkyl" means a saturated alicyclic moiety having from 3-8 carbon atoms and includes, for example, cyclohexyl, cyclooctyl, cycloheptyl, cyclopentyl, cyclobutyl and cyclopropyl.

The term "cycloalkenyl" means an unsaturated alicyclic moiety having from 4-8 carbon atoms and includes, for example, cyclohexenyl, cyclooctenyl, cycloheptenyl, cyclopentenyl, and cyclobutenyl. In the case of cycloalkenyl rings of from 5-8 carbon atoms, the ring may contain more than one double bond.

The term "aryl" means an unsaturated aromatic carbocyclic group which is moncyclic (eg phenyl) or polycyclic (eg naphthyl).

The unqualified term "heterocyclyl" or "heterocyclic" means (i) a 5-7 membered heterocyclic ring containing one or more heteroatoms selected from S, N and O, and optionally fused to a benzene ring, including for example, pyrrolyl, furyl, thienyl, piperidinyl, imidazolyl, oxazolyl, thiazolyl, thiadiazolyl, pyrazolyl, pyridinyl, pyrrolidinyl, pyrimidinyl, morpholinyl, piperazinyl, indolyl, benzimidazolyl, maleimido, succinimido, phthalimido, 1,2-dimethyl-3,5-dioxo-1,2,4-triazolidin-4-yl, 3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl, 2-methyl-3,5-dioxo-1,2,4-oxadiazol-4-yl, 3-methyl-2,4,5-trioxo-1-imidazolidinyl, 2,5-dioxo-3-phenyl-1-imidazolidinyl, 2-oxo-1-pyrrolidinyl, 2,5-dioxo-1-pyrrolidinyl or 2,6-dioxopiperidinyl, or (ii) a naphththalimido (ie 1,3-dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl), 1,3-dihydro-1-oxo-2H-benz[f]isoindol-2-yl, 1,3-dihydro-1,3-dioxo-2H-pyrrolo[3,4-b]quinolin-2-yl, or 2,3-dihydro-1,3-dioxo-1H-benz[d,e]isoquinolin-2-yl group.

The term "heteroaryl" means a 5-7 membered substituted or unsubstituted aromatic heterocycle containing one or more heteroatoms. Illustrative of such rings are thienyl, furyl, pyrrolyl, imidazolyl, thiazolyl, pyrazolyl, isoxazolyl, isothiazolyl, trizolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl and triazinyl.

The term "ester" or "esterified carboxyl group" means a group $R_9O(C=O)$- in which R_9 is the group characterising the ester, notionally derived from the alcohol R_9OH.

The term "thioester" means a group $R_9S(C=O)$- or $R_9S(C=S)$- or $R_9O(C=S)$-in which R_9 is the group characterising the thioester, notionally derived from the alcohol R_9OH

or the thioalcohol R_3SH.

Unless otherwise specified in the context in which it occurs, the term "substituted" as applied to any moiety herein means substituted with up to four substituents, each of which independently may be (C_1-C_6)alkyl, (C_1-C_6)alkoxy, hydroxy, mercapto, (C_1-C_6)alkylthio, amino, halo (including fluoro, chloro, bromo and iodo), nitro, trifluoromethyl, -COOH, $-CONH_2$, -CN, $-COOR^A$, $-CONHR^A$ or $-CONHR^AR^A$ wherein R^A is a (C_1-C_6)alkyl group or the residue of a natural alpha-amino acid.

The term "side chain of a natural or non-natural alpha-amino acid" means the group R^1 in a natural or non-natural amino acid of formula $NH_2-CH(R^1)-COOH$.

Examples of side chains of natural alpha amino acids include those of alanine, arginine, asparagine, aspartic acid, cysteine, cystine, glutamic acid, histidine, 5-hydroxylysine, 4-hydroxyproline, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, valine, α-aminoadipic acid, α-amino-n-butyric acid, 3,4-dihydroxyphenylalanine, homoserine, α-methylserine, ornithine, pipecolic acid, and thyroxine.

Natural alpha-amino acids which contain functional substituents, for example amino, carboxyl, hydroxy, mercapto, guanidyl, imidazolyl, or indolyl groups in their characteristic side chains include arginine, lysine, glutamic acid, aspartic acid, tryptophan, histidine, serine, threonine, tyrosine, and cysteine. When R_3 in the compounds of the invention is one of those side chains, the functional substituent may optionally be protected.

The term "protected" when used in relation to a functional substituent in a side chain of a natural alpha-amino acid means a derivative of such a substituent which is substantially non-functional. For example, carboxyl groups may be esterified (for example as a C_1-C_6 alkyl ester), amino groups may be converted to amides (for example as a $NHCOC_1-C_6$ alkyl amide) or carbamates (for example as an

NHC(=O)OC$_1$-C$_6$ alkyl or NHC(=O)OCH$_2$Ph carbamate), hydroxyl groups may be converted to ethers (for example an OC$_1$-C$_6$ alkyl or a O(C$_1$-C$_6$ alkyl)phenyl ether) or esters (for example a OC(=O)C$_1$-C$_6$ alkyl ester) and thiol groups may be converted to thioethers (for example a tert-butyl or benzyl thioether) or thioesters (for example a SC(=O)C$_1$-C$_6$ alkyl thioester).

Examples of side chains of non-natural alpha amino acids include those referred to below in the discussion of suitable R_3 groups for use in compounds of the present invention.

Salts of the compounds of the invention include physiologically acceptable acid addition salts for example hydrochlorides, hydrobromides, sulphates, methane sulphonates, p-toluenesulphonates, phosphates, acetates, citrates, succinates, lactates, tartrates, fumarates and maleates. Salts may also be formed with bases, for example sodium, potassium, magnesium, and calcium salts.

There are several chiral centres in the compounds according to the invention because of the presence of asymmetric carbon atoms. The presence of several asymmetric carbon atoms gives rise to a number of diastereomers with R or S stereochemistry at each chiral centre. All such diastereomers and mixtures thereof are included within the scope of the invention.

As previously stated, the compounds with which the present invention is concerned are principally distinguished from the compounds disclosed in the prior patent publications listed above by the ester or thioester group R_4. Accordingly the groups R, R_1, R_1, R_2, and R_3, may include those which have been disclosed in the corresponding positions of compounds disclosed in any of those prior art patent publications listed above. Without limiting the generality of the foregoing, examples of substituents R, to R_4 are given below:

The group R_1

R_1 may be, for example,

hydrogen, methyl, ethyl, n-propyl, n-butyl, isobutyl, allyl, phenylpropyl, cyclopropylmethyl, phenylprop-2-enyl, thienylsulphanylmethyl, thienylsulphinylmethyl, or thienylsulphonylmethyl; or

C_1-C_4 alkyl, eg methyl, ethyl n-propyl or n-butyl, substituted by a phthalimido, 1,2-dimethyl-3,5-dioxo-1,2,4-triazolidin-4-yl, 3-methyl-2,5-dioxo-1-imidazolidinyl, 3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl, 2-methyl-3,5-dioxo-1,2,4-oxadiazol-4-yl, 3-methyl-2,4,5-trioxo-1-imidazolidinyl, 2,5-dioxo-3-phenyl-1-imidazolidinyl, 2-oxo-1-pyrrolidinyl, 2,5-dioxo-1-pyrrolidinyl or 2,6-dioxopiperidinyl, 5,5-dimethyl-2,4-dioxo-3-oxazolidinyl, hexahydro-1,3-dioxopyrazolo[1,2,a][1,2,4]-triazol-2-yl, or a naphththalimido (ie 1,3-dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl), 1,3-dihydro-1-oxo-2H-benz[f]isoindol-2-yl, 1,3-dihydro-1,3-dioxo-2H-pyrrolo[3,4-b]quinolin-2-yl, or 2,3-dihydro-1,3-dioxo-1H-benz[d,e]isoquinolin-2-yl group; or

cyclohexyl, cyclooctyl, cycloheptyl, cyclopentyl, cyclobutyl, cyclopropyl, tetrahydropyranyl or morpholinyl.

Presently preferred R_1 groups include hydrogen, cyclopropylmethyl, n-propyl, and allyl.

The group R_2

R_2 may for example be

C_1-C_{12} alkyl, C_3-C_6 alkenyl or C_3-C_6 alkynyl;

cycloalkyl(C_1-C_6 alkyl)-;

phenyl(C_1-C_6 alkyl)-, phenyl(C_3-C_6 alkenyl)- or phenyl(C_3-C_6 alkynyl)- optionally substituted in the phenyl ring;

heteroaryl(C_1-C_6 alkyl)-, heteroaryl(C_3-C_6 alkenyl)- or heteroaryl(C_3-C_6 alkynyl)- optionally substituted in the heteroaryl ring;

4-phenylphenyl(C_1-C_6 alkyl)-, 4-phenylphenyl(C_3-C_6 alkenyl)-, 4-phenylphenyl(C_3-C_6 alkynyl)- , 4-heteroarylphenyl(C_1-C_6 alkyl)-, 4-heteroarylphenyl(C_3-C_6 alkenyl)-, 4-heteroarylphenyl(C_3-C_6 alkynyl)-, optionally substituted in the terminal phenyl or heteroaryl ring;

phenoxy(C_1-C_6 alkyl)- or heteroaryloxy(C_1-C_6 alkyl)- optionally substituted in the phenyl or heteroaryl ring;

Specific examples of such groups include methyl, ethyl, n- or iso-propyl, n-, iso- or tert-butyl, n-pentyl, n-hexyl, n-heptyl, n-nonyl, n-decyl, prop-2-yn-1-yl, cyclohexylethyl, cyclopentylmethyl, 3-phenylprop-2-yn-1-yl, 3-(2-chlorophenyl)prop-2-yn-1-yl, benzyl phenylpropyl, 4-chlorophenylpropyl, 4-methylphenylpropyl, 4-methoxyphenylpropyl, phenoxybutyl, 3-(4-pyridylphenyl)propyl-, 3-(4-(4-pyridyl)phenyl)prop-2-yn-1-yl, 3-(4-phenylphenyl)propyl-, 3-(4-phenyl)phenyl)prop-2-yn-1-yl and 3-[(4-chlorophenyl)phenyl]propyl-.

Presently preferred R_2 groups include benzyl, n-butyl, iso-butyl, n-hexyl, and cyclopentylmethyl

The group R_3

R_3 may for example be C_1-C_6 alkyl, phenyl, 2,- 3-, or 4-pyridyl, 2- or 3-thienyl, 2,- 3-, or 4-hydroxyphenyl, 2,- 3-, or 4-methoxyphenyl, 2,- 3-, or 4-pyridylmethyl, benzyl, 2,- 3-, or 4-hydroxybenzyl, 2,- 3-, or 4-benzyloxybenzyl, 2,- 3-, or 4-C_1-C_6 alkoxybenzyl, or benzyloxy(C_1-C_6alkyl)-.; or

the characterising group of a natural α–amino acid, in which any functional group may be protected, any amino group may be acylated and any carboxyl

group present may be amidated; or

a group -[Alk]$_n$R$_6$ where Alk is a (C_1-C_6)alkyl or (C_2-C_6)alkenyl group optionally interrupted by one or more -O-, or -S- atoms or -N(R_7)- groups [where R_7 is a hydrogen atom or a (C_1-C_6)alkyl group], n is 0 or 1, and R_6 is an optionally substituted cycloalkyl or cycloalkenyl group; or

a benzyl group substituted in the phenyl ring by a group of formula -OCH_2COR_8 where R_8 is hydroxyl, amino, (C_1-C_6)alkoxy, phenyl(C_1-C_6)alkoxy, (C_1-C_6)alkylamino, di((C_1-C_6)alkyl)amino, phenyl(C_1-C_6)alkylamino, the residue of an amino acid or acid halide, ester or amide derivative thereof, said residue being linked via an amide bond, said amino acid being selected from glycine, α or β alanine, valine, leucine, isoleucine, phenylalanine, tyrosine, tryptophan, serine, threonine, cysteine, methionine, asparagine, glutamine, lysine, histidine, arginine, glutamic acid, and aspartic acid; or

a heterocyclic(C_1-C_6)alkyl group, either being unsubstituted or mono- or di-substituted in the heterocyclic ring with halo, nitro, carboxy, (C_1-C_6)alkoxy, cyano, (C_1-C_6)alkanoyl, trifluoromethyl (C_1-C_6)alkyl, hydroxy, formyl, amino, (C_1-C_6)alkylamino, di-(C_1-C_6)alkylamino, mercapto, (C_1-C_6)alkylthio, hydroxy(C_1-C_6)alkyl, mercapto(C_1-C_6)alkyl or (C_1-C_6)alkylphenylmethyl; or

a group -$CR_aR_bR_c$ in which:

each of R_a, R_b and R_c is independently hydrogen, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, phenyl(C_1-C_6)alkyl, (C_3-C_8)cycloalkyl; or

R_c is hydrogen and R_a and R_b are independently phenyl or heteroaryl such as pyridyl; or

R_c is hydrogen, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, phenyl(C_1-

C_6)alkyl, or (C_3-C_8)cycloalkyl, and R_a and R_b together with the carbon atom to which they are attached form a 3 to 8 membered cycloalkyl or a 5- to 6-membered heterocyclic ring; or

R_a, R_b and R_c together with the carbon atom to which they are attached form a tricyclic ring (for example adamantyl); or

R_a and R_b are each independently (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, phenyl(C_1-C_6)alkyl, or a group as defined for R_c below other than hydrogen, or R_a and R_b together with the carbon atom to which they are attached form a cycloalkyl or heterocyclic ring, and R_c is hydrogen, -OH, -SH, halogen, -CN, -CO_2H, (C_1-C_4)perfluoroalkyl, -CH_2OH, -CO_2(C_1-C_6)alkyl, -O(C_1-C_6)alkyl, -O(C_2-C_6)alkenyl, -S(C_1-C_6)alkyl, -SO(C_1-C_6)alkyl, -SO_2(C_1-C_6) alkyl, -S(C_2-C_6)alkenyl, -SO(C_2-C_6)alkenyl, -SO_2(C_2-C_6)alkenyl or a group -Q-W wherein Q represents a bond or -O-, -S-, -SO- or -SO_2- and W represents a phenyl, phenylalkyl, (C_3-C_8)cycloalkyl, (C_3-C_8)cycloalkylalkyl, (C_4-C_8)cycloalkenyl, (C_4-C_8)cycloalkenylalkyl, heteroaryl or heteroarylalkyl group, which group W may optionally be substituted by one or more substituents independently selected from, hydroxyl, halogen, -CN, -CO_2H, -CO_2(C_1-C_6)alkyl, -$CONH_2$, -CONH(C_1-C_6)alkyl, -CONH(C_1-C_6alkyl)$_2$, -CHO, -CH_2OH, (C_1-C_4)perfluoroalkyl, -O(C_1-C_6)alkyl, -S(C_1-C_6)alkyl, -SO(C_1-C_6)alkyl, -SO_2(C_1-C_6)alkyl, -NO_2, -NH_2, -NH(C_1-C_6)alkyl, -N((C_1-C_6)alkyl)$_2$, -NHCO(C_1-C_6)alkyl, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_3-C_8)cycloalkyl, (C_4-C_8)cycloalkenyl, phenyl or benzyl.

Examples of particular R_3 groups include benzyl, phenyl, cyclohexylmethyl, pyridin-3-ylmethyl, tert-butoxymethyl, iso-propyl, iso-butyl, sec-butyl, tert-butyl, 1-benzylthio-1-methylethyl, 1-methylthio-1-methylethyl, and 1-mercapto-1-methylethyl.

Presently preferred R_3 groups include phenyl, benzyl, tert-butoxymethyl, iso-propyl

and iso-butyl.

The group R_4

Examples of particular ester and thioester groups R_4 groups include those of formula $-(C=O)OR_9$, $-(C=O)SR_9$, $-(C=S)SR_9$, and $-(C=S)OR_9$ wherein R_9 is (C_1-C_6)alkyl, (C_2-C_6)alkenyl, cycloalkyl, cycloalkyl(C_1-C_6)alkyl-, phenyl, heterocyclyl, phenyl(C_1-C_6)alkyl-, heterocyclyl(C_1-C_6)alkyl-, (C_1-C_6)alkoxy(C_1-C_6)alkyl-, (C_1-C_6)alkoxy(C_1-C_6)alkoxy(C_1-C_6)alkyl-, any of which may be substituted on a ring or non-ring carbon atom or on a ring heteroatom, if present. Examples of such R_9 groups include methyl, ethyl, n-and iso-propyl, n-, sec- and tert-butyl, 1-ethyl-prop-1-yl, 1-methyl-prop-1-yl, 1-methyl-but-1-yl, cyclopentyl, cyclohexyl, allyl, phenyl, benzyl, 2-, 3- and 4-pyridylmethyl, N-methylpiperidin-4-yl, 1-methylcyclopent-1yl, adamantyl, tetrahydrofuran-3-yl and methoxyethyl.

Presently preferred are compounds of formula (IB) wherein R_4 is a carboxylate ester of formula $-(C=O)OR_9$, wherein R_9 is benzyl, cyclopentyl, cyclohexyl, or isopropyl.

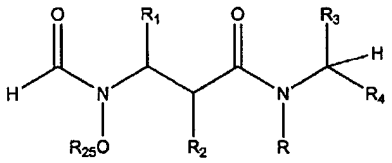
The group R

Presently preferred R groups are hydrogen and methyl.

Specific examples of compounds of the invention include those prepared according to the Examples below, and salts, hydrates and solvates thereof.

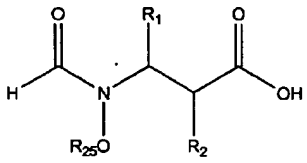
Compounds of the invention may be prepared by deprotecting an O-protected N-formyl-N-hydroxyamino compound of formula (II):

(II)

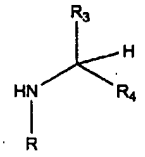


in which R_1, R_2, R_3 and R_4 are as defined in general formula (I) and R_{25} is a hydroxy protecting group removable to leave a hydroxy group by hydrogenolysis or hydrolysis. Benzyl is a preferred R_{25} group for removal by hydrogenolysis, and tetrahydropyranyl is a preferred group for removal by acid hydrolysis.

Compounds of formula (II) may be prepared by causing an acid of formula (III) or an activated derivative thereof to react with an amine of formula (IV)



(III)

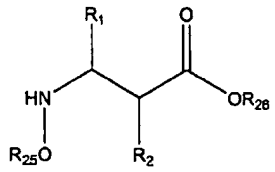


(IV)

wherein R_1, R_2, R_3 and R_4 are as defined in general formula (I) except that any substituents in R_1, R_2, R_3 and R_4 which are potentially reactive in the coupling reaction may themselves be protected from such reaction, and R_{25} is as defined in relation to formula (II) above, and optionally removing protecting groups from R_1, R_2, R_3 and R_4.

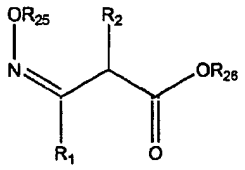
Compounds of formula (III) may be prepared by N-formylation, for example using acetic anhydride and formic acid, of compounds of formula (V)

(V)



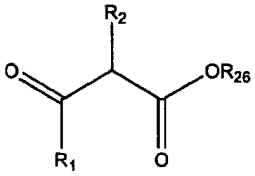
wherein R_1, R_2 and R_{25} are as defined in relation to formula (II) and R_{26} is a hydroxy protecting group, and thereafter removing the protecting group R_{26}.

A compound of general formula (V) may be prepared by reduction of an oxime of general formula (VI)

(VI) 

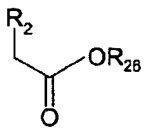
wherein R_1, R_2, R_{25} and R_{26} are as defined above. Reducing agents include metal hydrides (eg sodium cyanoborohydride in acetic acid, triethylsilane or borane/pyridine) and hydrogenation.

A compound of general formula (VI) can be prepared by reaction of a β-keto carbonyl compound of general formula (VII)

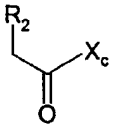
(VII) 

wherein R_1, R_2, and R_{26} are as defined above, with an O-protected hydroxylamine.

β-keto carbonyl compounds (VI) may be prepared by acylation of the enolate derived from a carbonyl compound of formula (VII) or (VIIA)

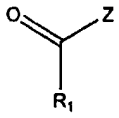


(VII)



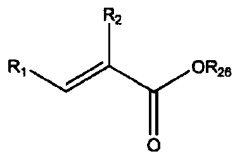
(VIIA)

wherein R_2 and R_{26} are as defined above, and X_c is a chiral auxiliary, with a compound of formula (VII)

(VII) 

wherein R_1 is as defined above and Z is a leaving group such as chloro or alkoxy. Chiral enolates of type (VIIA) have been described by Evans (J. Am. Chem. Soc., 104, 1737, (1982)).

Another method for the preparation of a compound of general formula (IV) is by Michael addition of a hydroxylamine derivative to an α, β-unsaturated carbonyl compounds of general formula (IX)

(IX) 

wherein R_1, R_2, and R_{26} are as defined above. The α,β-unsaturated carbonyl compounds (IX) may be prepared by standard methods.

The compounds with which the invention is concerned may be prepared for administration by any route consistent with their pharmacokinetic properties.

Orally administrable compositions may be in the form of tablets, capsules, powders, granules, lozenges, liquid or gel preparations, such as oral, topical, or sterile parenteral solutions or suspensions. Tablets and capsules for oral administration may be in unit dose presentation form, and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinyl-pyrrolidone; fillers for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tabletting lubricant, for example magnesium stearate, talc, polyethylene glycol or silica; disintegrants for example potato starch, or acceptable wetting agents such as sodium lauryl sulphate. The tablets may be

coated according to methods well known in normal pharmaceutical practice. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, glucose syrup, gelatin hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, fractionated coconut oil, oily esters such as glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and if desired conventional flavouring or colouring agents.

For topical application to the skin, the drug may be made up into a cream, lotion or ointment. Cream or ointment formulations which may be used for the drug are conventional formulations well known in the art, for example as described in standard textbooks of pharmaceutics such as the British Pharmacopoeia.

The active ingredient may also be administered parenterally in a sterile medium. Depending on the vehicle and concentration used, the drug can either be suspended or dissolved in the vehicle. Advantageously, adjuvants such as a local anaesthetic, preservative and buffering agents can be dissolved in the vehicle.

It will be understood that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

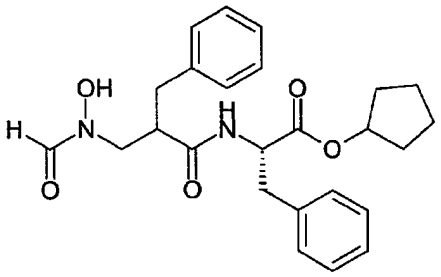
The following preparative Examples describe the preparation of compounds useful in accordance with the invention

The following abbreviations have been used in the examples

DCM - Dichloromethane
DMF - N,N-Dimethylformamide
HOBT - 1-Hydroxybenzotriazole
WSCDI - N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride
HCl - Hydrochloric acid
THF - Tetrahydrofuran

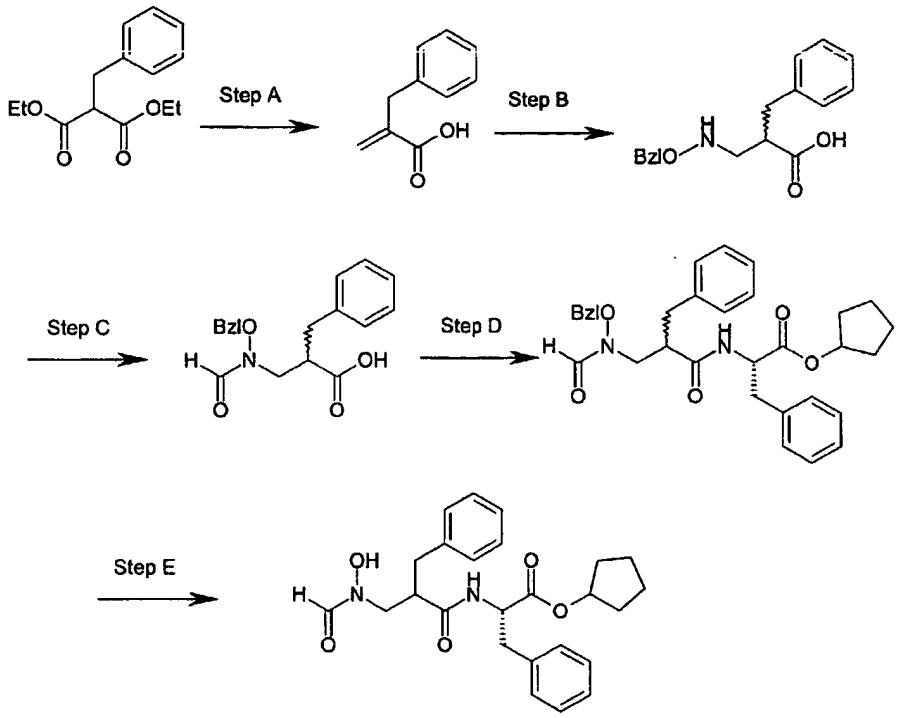
Example 1

2S-[2-(R,S)-Benzyl-3-(formyl-hydroxy-amino)-propionylamino]-3-phenyl-propionic acid cyclopentyl ester



Example 1 was prepared as outlined in Scheme 1 using procedures described below.

Scheme 1



Reagents and conditions: A. (1) EtOH/KOH/H_2O, reflux 5 hours, (2) piperidine, HCHO, EtOH, reflux 4 hours; B. H_2NOBzl, 80°C o/n; C. HCOOH, Ac_2O; D. WSCDI, HOBT, DMF, L-phenylalanine cyclopentyl ester r.t., 18 hours; E. $H_2(g)$, Pd catalyst, EtOH 90 minutes.

(a) 2-Benzyl-acrylic acid

Diethyl benzylmalonate (100g, 400mmol) was dissolved in ethanol (300mL) and treated with a solution of potassium hydroxide (134.4g, 2.4mol) in water (500mL). The mixture was heated under reflux for 5 hours and then allowed to cool. Ethanol was removed under reduced pressure and the remaining aqueous solution cooled in ice and acidified to pH1 with concentrated HCl. The product was extracted with ethyl acetate (3x200mL). The combined extracts were washed with brine, dried over magnesium sulphate, filtered and concentrated under reduced pressure to yield benzylmalonic acid as a white crystalline solid. The solid was taken-up in ethanol (250mL) and treated portionwise with piperidine (33g, 397mmol) followed by an aqueous solution of formaldehyde (37%, 150mL) which resulted in formation of a white precipitate. The reaction mixture was heated and treated with methanol (50mL) to give a homogeneous solution. Following dissolution the reaction mixture was heated under reflux for 4 hours. The reaction mixture was concentrated under reduced pressure. The aqueous residue was acidified to pH1 with 1M HCl and the product extracted with ethyl acetate (3x150mL). The combined extracts were washed with brine, dried over magnesium sulphate, filtered and concentrated under reduced pressure to yield 2-benzyl-acrylic acid as a colourless oil which crystallized on standing (45g, 75%). ^{1}H-NMR; δ ($CDCl_3$), 7.32-7.17 (5H, m), 6.36 (1H, s), 5.54 (1H, d, J=1.3Hz), 3.61 (2H, s).

(b) 2-(R,S)-Benzyl-3-benzyloxyamino-propionic acid

A mixture of 2-benzyl-acrylic acid (8.0g, 55mmol) and O-benzylhydroxylamine (16.0g, 130mmol) was heated at 80°C for 18 hours. The reaction mixture was cooled, diluted with diethyl ether (100mL) and extracted with 1M sodium carbonate (3x100mL). The combined aqueous extracts were acidified with 3M citric acid and then re-extracted with DCM (3x100mL). The combined organic extracts were washed with brine, dried over magnesium sulphate, filtered and concentrated under reduced pressure to yield 2-(R,S)-benzyl-3-benzyloxyamino-propionic acid as a

white crystalline solid (7.82g, 53%). ^{1}H-NMR; δ ($CDCl_3$), 7.61-7.15 (10H, m), 4.66 (2H, d, J=1.7Hz), 3.13-2.94 (4H, m), 2.84-2.74 (1H, m).

(c) 2-(R,S)-Benzyl-3-(benzyloxy-formyl-amino)-propionic acid

A solution of 2-(R,S)-benzyl-3-benzyloxyamino-propionic acid (7.8g, 27.4mmol) in formic acid (40mL) was cooled in an ice-water bath and treated dropwise with acetic anhydride (15mL). The reaction was allowed to warm to room temperature and stirred for 18 hours. The reaction mixture was diluted with DCM (150mL) and partitioned with water (100mL). The organic layer was separated, washed with brine, dried over magnesium sulphate, filtered and concentrated under reduced pressure to yield 2-(R,S)-benzyl-3-(benzyloxy-formyl-amino)-propionic acid as a colourless oil (7.8g, 91%). ^{1}H-NMR; δ ($CDCl_3$), 7.87-7.16 (10H, m), 4.92-4.66 (2H, m), 4.03-3.90 (2H, m), 3.17-2.93 (2H, m), 2.78-2.70 (1H, m).

(d) 2S-[2-(R,S)-Benzyl-3-(benzyloxy-formyl-amino)-propionylamino]-3-phenyl propionic acid cyclopentyl ester

2-(R,S)-Benzyl-3-(benzyloxy-formyl-amino)-propionic acid (2.89g, 9.3mmol) was dissolved in DMF (20mL) and treated with HOBT (1.35g, 10mmol) and WSCDI (1.91g, 10mmol). The reaction mixture was stirred at room temperature for 1 hour before the addition of a solution of L-phenylalanine cyclopentyl ester (2.4g, 10.3mmol) in DMF (10mL). The reaction mixture was stirred at room temperature for 18 hours. DMF was removed under reduced pressure and the residue partitioned between ethyl acetate and 1M HCl. The organic layer was separated and washed with 1M HCl, saturated aqueous sodium bicarbonate solution and brine before drying over magnesium sulphate, filtration and concentration under reduced pressure to yield 2S-[2-(R,S)-benzyl-3-(benzyloxy-formyl-amino)-propionylamino]-3-phenylpropionic acid cyclopentyl ester (3.6g used crude in step e).

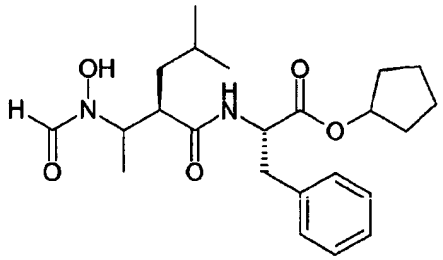
(e) 2S-[2-(R,S)-Benzyl-3-(formyl-hydroxy-amino)-propionylamino]-3-phenyl-propionic

acid cyclopentyl ester

A solution of 2S-[2-(R,S)-benzyl-3-(benzyloxy-formyl-amino)-propionylamino]-3-phenyl propionic acid cyclopentyl ester (3.6g crude from step d) in ethanol (30mL) was treated with a palladium catalyst (100mg, 10%Pd on charcoal). The reaction mixture was stirred under an atmosphere of hydrogen gas for 90 minutes. Catalyst was removed by filtration and the filtrate concentrated to a colourless oil. Using reverse phase chromatography 200mg of the crude product was fractionated to provide two diastereoisomers of 2S-[2-benzyl-3-(formyl-hydroxy-amino)-propionylamino]-3-phenyl-propionic acid cyclopentyl ester. Diastereoisomer A (35mg), ^{1}H-NMR; δ ($CDCl_3$), 8.34 and 7.77 (1H, 2xs), 7.29-6.84 (10H, m), 6.13 (1H, d, J=7.3Hz), 5.11-5.00 (1H, m), 4.67-4.49 (1H, m), 3.99-3.79 (1H, m), 3.66-3.60 and 3.51-3.47 (1H, 2xm), 3.05-2.69 (5H, m) and 1.85-1.45 (8H, m); ^{13}C-NMR; δ($CDCl_3$), 174.4, 172.3, 171.4, 171.2, 138.2, 136.3, 129.8, 129.6, 129.2, 128.9, 127.5, 127.4, 127.2, 79.4, 78.9, 54.3, 54.0, 51.9, 51.1, 48.8, 47.9, 46.6, 38.7, 38.1, 36.8, 36.5, 33.0, 32.8 and 24.0. Diastereoisomer B (42mg), ^{1}H-NMR; δ ($CDCl_3$), 8.35 and 7.71 (1H, 2xs), 7.33-7.15 (8H, m), 7.08-6.94 (1H, bm), 6.83-6.73 (2H, m), 6.20 and 5.94 (2xd), 5.30-5.08 (1H, m), 4.73-4.64 (1H, m), 3.85-3.76 (1H, m), 3.56-3.47 (1H, m), 3.01-2.68 (5H, m) and 1.91-1.45 (8H, m); ^{13}C-NMR; δ($CDCl_3$), 174.2, 172.9, 172.4, 171.8, 138.7, 136.1, 129.6, 129.3, 129.1, 128.9, 128.8, 127.6, 127.5, 127.4, 127.3, 127.2, 127.1, 79.9, 79.2, 53.9, 53.6, 52.3, 50.3, 48.1, 47.0, 38.3, 37.5, 36.9, 36.4, 32.9, 32.8 and 24.0.

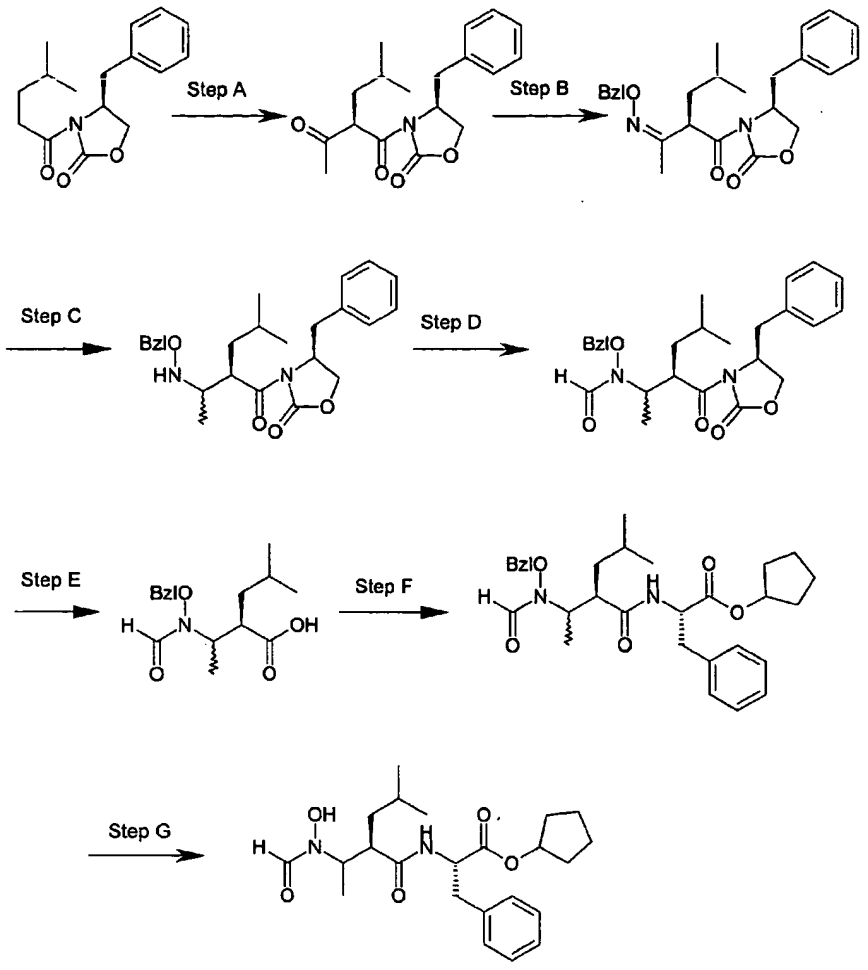
Example 2

2S-{2R-[1-(R,S)-(Formyl-hydroxy-amino)-ethyl]-4-methyl-pentanoylamino}-3-phenylpropionic acid cyclopentyl ester



Example 2 was prepared as outlined in scheme 2 using procedures described below.

Scheme 2



Reagents and conditions: A. Sodium hexamethyldisilazide, AcCl, -60°C 3 hours; B. $BzlONH_2$ HCl, NaOAc, H_2O/EtOH, 50°C 18 hours; C. AcOH, $NaCNBH_3$, 25 hours; D. HCOOH, AcOH, 18 hours; E. LiOH, H_2O_2, THF/H_2O, 4 hours; F. L-Phenylalanine cyclopentyl ester, HOBT, WSCDI, DMF, 48 hours, G. H_2(g), Pd catalyst, EtOH, 2 hours.

(a) 1-(4S-Benzyl-2-oxo-oxazolidin-3-yl)-2R-isobutyl-butane-1,3-dione

A solution of 4S-benzyl-3-(4-methyl-pentanoyl)-oxazolidin-2-one (31g, 113mmol) in anhydrous THF (750mL) was cooled to -70°C under an inert atmosphere. Sodium hexamethyldisilazide (118mL of a 1M solution, 118mmol) was added via cannula whilst maintaining the temperature below -68°C. The reaction mixture was stirred at -70°C for 30 minutes before the addition of acetyl chloride (10.2mL, 135mmol), again maintaining the temperature below -68°C. The reaction was slowly warmed to -60°C and maintained at this temperature for 3 hours before quenching with acetic acid (6.75g, 118mmol) in diethyl ether (10mL). The solvent was removed under reduced pressure and the resulting slurry taken up in ethyl acetate and washed with brine. The organic layer was dried over sodium sulphate, filtered and concentrated under reduced pressure to leave an oil (36g) which was shown by NMR to contain the title compound contaminated with 15% of the starting material. ^{1}H-NMR; δ ($CDCl_3$), 7.35-7.22 (5H, m), 4.69-4.65 (1H, m), 4.63-4.57 (1H, dd, J=3.2Hz), 4.22-4.13 (2H, m), 3.41 (1H, dd, J=3.2Hz), 2.74 (1H, dd, J=9.8Hz), 2.31 (3H, s), 2.10-2.04 (1H, m), 1.68-1.60 (1H, m), 1.49-1.39 (1H, m) and 0.97 (6H, 2xd, J=6.5Hz).

(b) 1-(4S-Benzyl-2-oxo-oxazolidin-3-yl)-2R-isobutyl-butane 1,3-dione 3-(O-benzyl-oxime)

1-(4S-Benzyl-2-oxo-oxazolidin-3-yl)-2R-isobutyl-butane-1,3-dione (35.5g, 112mmol) was dissolved in water/ethanol (500mL, 10%vol/vol) and treated with benzylhydroxylamine hydrochloride (21.4g, 134mmol) and sodium acetate (18.3g, 134mmol). The reaction mixture was stirred at 50°C for 18 hours. The solution was concentrated under reduced pressure to give a white precipitate of the product which was collected by filtration (21.0g, 44%). ^{1}H-NMR; δ ($CDCl_3$), 7.38-7.08 (10H, m), 5.15-5.04 (2H, m), 4.57-4.47 (1H, m), 4.24 (1H, dd, J=3.6Hz), 4.07 (1H, dd, J=8.9Hz), 3.92 (1H, dd, J=2.6Hz), 3.16 (1H, dd, J=2.7Hz), 2.09 (3H, s), 2.04-1.98 (1H, m), 1.76-1.66 (1H, dd, J=11.0Hz), 1.63-1.60 (1H, m), 1.45-1.35 (1H, m) and 0.94 (6H, 2xd, J=6.6Hz).

(c) 4S-Benzyl-3-[2R-(1-(R,S)-benzyloxyamino-ethyl)-4-methyl-pentanoyl]-oxazolidin-2-one

1-(4S-Benzyl-2-oxo-oxazolidin-3-yl)-2R-isobutyl-butane 1,3-dione 3-(O-benzyl-oxime) (21g, 50mmol) was dissolved in acetic acid (400mL) and sodium cyanoborohydride (6.24g, 100mmol) added portionwise. The mixture was stirred for 18 hours at room temperature then a further equivalent of sodium cyanoborohydride added. Stirring was continued for a further 7 hours then the reaction mixture concentrated under reduced pressure. The resultant oil was taken up in DCM (600mL) then carefully washed with sodium carbonate and brine. The organic layer was dried over magnesium sulphate, filtered and evaporated to a colourless oil (21g). Column chromatography on silica gel using DCM as eluent lead to isolation of the desired product as a mixture of diastereoisomers (9.05g, 43%). ^{1}H-NMR; δ ($CDCl_3$), 7.37-7.18 (10H, m), 5.80 (1H, bs), 4.70-4.60 (3H, m), 4.13 (1H, m), 4.12-4.05 (2H, m), 3.91 (1H, m), 3.43-3.36 (1H, m), 2.48-2.37 (1H, m), 2.00-1.75 (1H, m), 1.70-1.64 (1H, m), 1.40-1.31 (1H, m), 1.24 (3H, m) and 0.94-0.87 (6H, m).

(d) N-[2-(4S-Benzyl-2-oxo-oxazolidine-3S-carbonyl)-1-(R,S),4-dimethyl-pentyl]-N-benzyloxyformamide

4S-Benzyl-3-[2R-(1-(R,S)-benzyloxyamino-ethyl)-4-methyl-pentanoyl]-oxazolidin-2-one (12.7g, 30mmol) was taken up in formic acid (250mL) and stirred at 0°C while acetic anhydride (50mL) was added dropwise. The mixture was stirred at room temperature for 18 hours. The reaction mixture was concentrated under reduced pressure, taken up in DCM and washed with saturated sodium bicarbonate and brine. The solution was dried over magnesium sulphate, filtered and concentrated to yield the title compound as a colourless oil (12.7g, 94%). ^{1}H-NMR; δ ($CDCl_3$, mixture of diastereoisomers), 8.35 and 8.14 (1H, 2xbs), 7.55-7.15 (10H, m), 5.20-4.90 (2H, bm), 4.73-4.46 (2H, m), 4.20-4.01 (3H, m), 3.31 (1H, dt, J=13.2, 3.2Hz), 2.51-2.30 (1H, m), 1.95-1.74 (1H, bm), 1.54-1.33 (5H, bm), 0.98-0.85 (6H, m).

(e) 2R-[1-(R,S)-(Benzyloxy-formyl-amino)-ethyl]-4-methyl-pentanoic acid

N-[2-(4S-Benzyl-2-oxo-oxazolidine-3S-carbonyl)-1-(R,S),4-dimethyl-pentyl]-N-benzyloxyformamide (7.30g, 16.1mmol) was dissolved in THF (210mL) and water (60mL) and cooled to 0°C. Hydrogen peroxide (1.84mL, 30% solution, 64.5mmol) was added dropwise followed by aqueous lithium hydroxide (1.02g in10mL, 24.2mmol) and the solution stirred at 0°C for 4 hours. The reaction mixture was quenched by the addition of sodium nitrite (1.11g, 16mmol). THF was removed under reduced pressure and the chiral auxilliary removed by extraction into DCM. The aqueous solution was was neutralised (pH5) with 1M HCl and extracted with ethyl acetate. The combined extracts were dried over magnesium sulphate, filtered and concentrated to yield the product as a yellow oil (3.78g, 80%). ^{1}H-NMR; δ ($CDCl_3$, mixture of diastereoisomers), 8.40 and 8.00 (1H, 2xs), 7.52-7.26 (5H, m), 5.25-4.85 (2H, 2xbd), 4.45 (1H, m), 3.85 (1H, bm), 2.90 (1H, bm), 1.75-1.48 (2H, bm), 1.48-1.20 (4H, bm) and 1.00-0.84 (6H, m).

(f) 2S-{2R-[1-(R,S)-(Benzyloxy-formyl-amino)-ethyl]-4-methyl-pentanoylamino}-3-phenyl-propionic acid cyclopentyl ester

A solution of 2R-[1-(R,S)-(benzyloxy-formyl-amino)-ethyl]-4-methyl-pentanoic acid (410mg, 1.40mmol) in DMF (10mL) was treated with HOBT (227mg, 1.68mmol) and WSCDI (322mg, 1.68mmol). A solution of L-phenylalanine cyclopentyl ester (394mg, 1.68mmol) in DMF (2mL) was added to the reaction mixture. The reaction was stirred at room temperature for 48 hours. DMF was removed by evaporation under reduced pressure. The residue was taken up in ethyl acetate and washed with 1M HCl, saturated sodium bicarbonate and brine, before drying over magnesium sulphate, filtration and concentration to a colourless oil. The product was purified by column chromatography on silica gel eluting with 20-40% ethyl acetate/hexane. Product containing fractions were combined and solvent evaporated to provide the title compound as an off-white foam (571mg, 66%). ^{1}H-NMR; δ ($CDCl_3$, mixture of diastereoisomers), 8.19 and 7.97 (1H, 2xs), 7.50-6.90

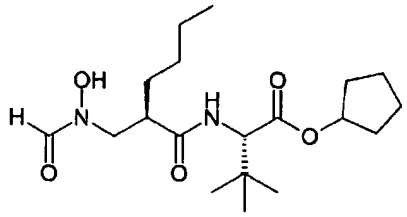
(10H, m), 6.09 and 5.94 (1H, 2xbd), 5.34-5.02 (2H, m), 4.95-4.74 (2H, m), 3.91-3.61 (2H, 2xbm), 3.15-2.80 (2H, m), 2.80-2.60 and 2.55-2.35 (1H, 2xm), 1.92-1.35 (11H, m), 1.22-1.00 (2H, m), 0.95-0.82 (6H, m).

(g) 2S-{2R-[1-(R,S)-(Formyl-hydroxy-amino)-ethyl]-4-methyl-pentanoylamino}-3-phenylpropionic acid cyclopentyl ester

A solution of 2S-{2R-[1-(R,S)-(benzyloxy-formyl-amino)-ethyl]-4-methyl-pentanoyl amino}-3-phenyl-propionic acid cyclopentyl ester (447mg, 0.88mmol) in ethanol (25mL) was treated with palladium catalyst (89mg, 10% Pd on charcoal) as a slurry in ethyl acetate (2mL). Hydrogen gas was bubbled through the resulting suspension for 2 hours. The catalyst was removed by filtration and the filtrate concentrated under reduced pressure to a white foam. The reaction product was separated by preparative reverse phase chromatography to yield two diastereoisomers. Diastereoisomer A (41mg, 11%), ^{1}H-NMR; δ (methanol-d_4), 8.60 (0.6H, d, J=8.2Hz), 8.52 (0.4H, d, J=8.2Hz), 8.24 (0.4H, s), 7.90 (0.6H, s), 7.84-7.15 (5H, m), 5.15 (1H, m), 4.79-4.71 (1H, m), 4.34-4.22 (0.4H, m), 3.66-3.54 (0.7H, m), 3.25-3.15 (1H, m), 2.90 (1H, dd, J=14.0, 10.4Hz), 2.70-2.56 (1H, m), 1.87-1.40 (10H, bm), 1.13-0.97 (1H, m) and 0.91-0.75 (9H, bm); ^{13}C-NMR; δ(methanol-d_4), 175.9, 172.8, 138.4, 130.2, 129.5, 127.9, 59.0, 55.2, 55.1, 54.2, 48.8, 40.4, 40.2, 38.3, 33.5, 26.6, 26.5, 24.7, 24.6, 21.7, 17.1 and16.0. Diastereoisomer B (28mg, 8%), ^{1}H-NMR; δ (methanol-d_4), 7.95 (0.4H, s), 7.84 (0.6H, s), 7.26-7.21 (5H, m), 5.13 (0.4H, m), 5.04 (0.6H, m), 4.73-4.66 (0.4H, m), 4.62-4.56 (0.6H, m), 4.42-4.36 (0.4H, m), 3.89-3.78 (0.6H, m), 3.18-2.61 (3H, bm), 1.77-1.44 (10H, m), 1.29-1.11 (3H, m), 1.00-0.87 (7H, m); ^{13}C-NMR; δ(methanol-d_4), 172.7, 138.0, 130.4, 129.5, 127.9, 79.6, 59.0, 53.3, 49.6, 39.9, 38.8, 38.4, 33.5, 33.4, 27.1, 26.7, 24.7, 24.6, 24.3, 24.1, 22.1, 21.9, 16.2 and 15.2.

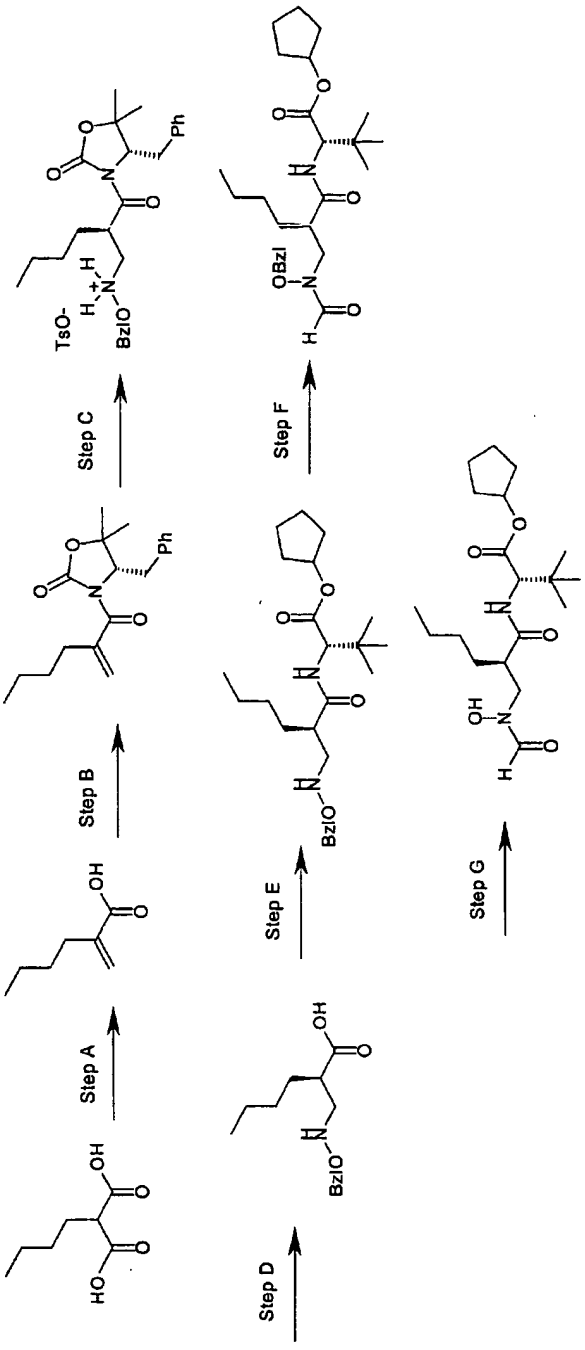
Example 3

2S-{2R-[(Formyl-hydroxy-amino)-methyl]-hexanoylamino}-3,3-dimethyl butyric acid cyclopentyl ester



The title compound was prepared as outlined in Scheme 3 and is described in detail below:

Scheme 3



Reagents and conditions: A. piperidine, HCHO, EtOH, 80°C, o/n; B. ^{t}BuCOCl, Et_3N then 3-lithio-4-benzyl-5,5-dimethyl-oxazolidin-2-one; C. H_2NOBzl, room temp., o/n then pTsOH, EtOAc; D. LiOH, aq THF, 0°C; E. H-t-Leu-OcPentyl, HOBt, EDC, DMF; F. HCOBt, THF; G. H_2, Pd/C, EtOH.

Step A: 2-Butyl acrylic acid

To a solution of n-butylmalonic acid (17.2g, 107mmol) in ethanol (200ml) was added piperidine (12.76ml, 129mmol) and 37% aq. formaldehyde (40.3 ml, 538mmol). The solution was heated to 80°C during which time a precipitate appeared and then gradually redissolved over 1 hour. The reaction mixture was stirred at 80°C overnight then cooled to room temperature. The solvents were removed under reduced pressure and the residue was dissolved in ethyl acetate (200ml), washed successively with 1M hydrochloric acid and brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated to give the title compound as a clear oil (13.37g, 97%). ^{1}H-NMR; δ ($CDCl_3$), 6.29 (1H, s), 5.65 (1H, s), 2.34-2.28 (2H, m), 1.54-1.26 (4H, m) and 0.94 (3H, t, J=7.1Hz).

Step B: 4S-Benzyl-3-(2-butyl-acryloyl)-5,5-dimethyl-oxazolidin-2-one

2-Butyl acrylic acid (21.5g, 168mmol) was dissolved in dry THF (500ml) and cooled to -78°C under a blanket of argon. Triethylamine (30ml, 218mmol) and pivaloyl chloride (21ml, 168mmol) were added at such a rate that the temperature remained below -60°C. The mixture was stirred at -78°C for 30 minutes, warmed to room temperature for 2 hours and finally cooled back to -78°C.

In a separate flask, 4S-benzyl-5,5-dimethyl-oxazolidin-2-one was dissoved in dry THF (500ml) and cooled to -78°C under a blanket of argon. n-Butyllithium (2.4M solution in hexanes, 83ml, 200mmol) was added slowly and the mixture was stirred for 30 minutes at room temperature. The resulting anion was tranferred via a cannula into the original reaction vessel. The mixture was allowed to warm to room temperature and stirred overnight at room temperature. The reaction was quenched with 1M potassium hydrogen carbonate (200ml) and the solvents were removed under reduced pressure. The residue was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried over anhydrous magnesium sulphate, filtered and concentrated under reduced pressure to an orange oil. TLC

analysis revealed the presence of unreacted chiral auxiliary in addition to the required product. A portion of the material (30g) was dissolved in dichloromethane and flushed though a silica pad to give pure title compound as a yellow oil (25.3g). ^{1}H-NMR;δ ($CDCl_3$), 7.31-7.19 (5H, m), 5.41 (2H,s), 4.51 (1H, dd, J=9.7, 4.2Hz), 3.32 (1H, dd, J=14.2, 4.2Hz), 2.82 (1H, dd, J=14.2, 9.7Hz), 2.40-2.34 (2H, m), 1.48-1.32 (4H, m), 1.43 (3H, s), 1.27 (3H, s) and 0.91 (3H, t, J=7.1Hz). Some chiral auxiliary was recovered by flushing the silica pad with methanol.

Step C: 4S-Benzyl-3-[2-(benzyloxyamino-methyl)-hexanoyl]-5,5-dimethyl-oxazolidin-2-one (p-toluenesulfonic acid salt)

4S-Benzyl-3-(2-butyl-acryloyl)-5,5-dimethyl-oxazolidin-2-one (19.8g, 62.8mmol) was mixed with O-benzylhydroxylamine (15.4g, 126mmol) and stirred overnight at room temperature. The mixture was dissolved in ethyl acetate and the solution was washed with 1M hydrochloric acid, 1M sodium carbonate and brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure to a pale yellow oil (25.3g) which was shown by NMR and HPLC analysis to contain 4S-Benzyl-3-[2-(benzyloxyamino-methyl)-hexanoyl]-5,5-dimethyl-oxazolidin-2-one (ca. 82% d.e.) along with a trace of starting material. The product was combined with a another batch (26.9g, 76% d.e.) and dissolved in ethyl acetate (200ml). p-Toluenesulfonic acid (22.7g, 119mmol) was added and the mixture was cooled to 0°C. The title compound was obtained as a white crytalline solid by seeding and scratching. Yield: 25.2g, (34%, single diastereoisomer). A second crop (14.7g, 20%, single diastereoisomer) was also obtained. ^{1}H-NMR;δ ($CDCl_3$), 7.89 (2H, d, J=8.2Hz), 7.37-7.12 (10H, m), 7.02 (2H, d, J=6.9Hz), 5.28-5.19 (2H,m), 4.55 (1H, m), 4.23 (1H, m), 3.93 (1H, m), 3.58 (1H, m), 2.58 (1H, m), 2.35 (3H, s), 1.67-1.51 (2H, m), 1.29-1.16 (4H, m), 1.25 (3H, s), 1.11 (3H, s) and 0.80-0.75 (3H, m).

Step D: 2R-Benzyloxyamino-methyl)-hexanoic acid

4S-Benzyl-3-[2R-(benzyloxyamino-methyl)-hexanoyl]-5,5-dimethyl-oxazolidin-2-one

p-toluenesulfonic acid salt (25.2g, 40.2mmol) was partitioned between ethyl acetate and 1M sodium carbonate. The organic phase was dried over anhydrous magnesium sulfate, filtered and evaporated under reduced pressure. The residual oil was dissolved in THF (150ml) and water (50ml) and cooled to 0°C and treated with lithium hydroxide (1.86g, 44.2mmol). The solution was stirred for 30 minutes at 0°C, then overnight at room temperature. The reaction was acidified to pH4 with 1M citric acid and the solvents were removed. The residue was partitioned between dichloromethane and 1M sodium carbonate. The basic aqueous layer was acidified to pH4 with 1M citric acid and extracted three times with ethyl acetate. The combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated to provide the title compound as a colourless oil (7.4g, 73%). ^{1}H-NMR;δ ($CDCl_3$), 8.42 (2H, br s), 7.34-7.25 (5H, m), 4.76-4.66 (2H, m), 3.20-3.01 (2H, m), 2.73 (1H, m), 1.70-1.44 (2H, m), 1.34-1.22 (4H, m) and 0.92-0.86 (3H, m).

Step E: 2S-[2R-(Benzyloxyamino-methyl)-hexanoylamino]-3,3-dimethyl butyric acid cyclopentyl ester

2R-Benzyloxyamino-methyl)-hexanoic acid (1.99g, 7.93mmol) was dissolved in DMF (50ml) and the solution was cooled to 0°. EDC (874mg, 4.56mmol) and HOBt (62mg, 0.46mmol) were added and the mixture was stirred for 15 minutes. *tert*-Leucine cyclopentyl ester (1.0g, 5.02mmol) was added and the reaction was allowed to warm to room temperature and stirred overnight. The solvent was removed under reduced pressure and the residue was dissolved in ethyl acetate, washed successively with 1M hydrochloric acid, saturated sodium hydrogen carbonate and brine, dried and filtered. The solvent was removed to leave a yellow oil which was purified by flash chromatography (silica gel, 20% ethyl acetate in hexane) to afford the title compound (964mg, 28%) ^{1}H-NMR;δ ($CDCl_3$), 7.36-7.29 (5H, m), 6.62 (1H, br d, J=9.2Hz), 5.69 (1H, br s), 5.22-5.18 (1H, m), 4.73 (2H, s), 4.42 (1H, d, J=9.4Hz), 3.11-3.04 (2H,m), 2.51 (1H, m), 1.87-1.59 (10H, m), 1.30-1.23 (4H, m), 0.97 (9H, s) and 0.87 (3H, t, J=6.7Hz).

Step F: 2S-{2R-[(Benzyloxy-formyl-amino)-methyl]-hexanoylamino}-3,3-dimethyl butyric acid cyclopentyl ester

2S-[2R-(Benzyloxyamino-methyl)-hexanoylamino]-3,3-dimethyl butyric acid cyclopentyl ester (947mg, 2.19mmol) was dissolved in dry THF (40ml) and treated with 1-formyl-benzotriazole (354mg, 2.41mmol). The reaction was stirred overnight at room temperature. The solvent was removed under reduced pressure and the residue was dissolved in ethyl acetate and washed with 1M sodium carbonate solution and brine. The organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated to dryness under reduced pressure. The desired product was obtained by flash chromatography (silica gel, eluting with 25% ethyl acetate in hexane). Yield: 814mg (81%) . ^{1}H-NMR;δ ($CDCl_3$, rotamers), 8.13 (0.7H, br s), 7.88 (0.3H, br s), 7.37 (5H, br s), 6.02 (1H, br d, J=9.1Hz), 5.18 (1H, m), 4.96 (1H, br s), 4.76 (1H, br s), 4.35 (1H, d, J=9.2Hz), 3.74 (2H, br s), 2.53 (1H, m), 1.87-1.59 (10H, m), 1.28-1.23 (4H, m), 0.96-0.84 (3H, m) and 0.93 (9H, s).

Step G: 2S-{2R-[(Formyl-hydroxy-amino)-methyl]-hexanoylamino}-3,3-dimethyl butyric acid cyclopentyl ester

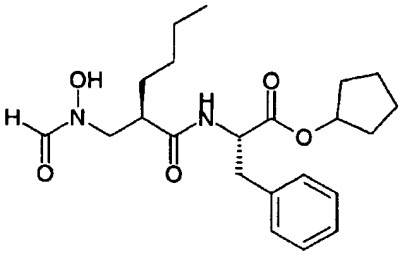
2S-{2R-[(Benzyloxy-formyl-amino)-methyl]-hexanoylamino}-3,3-dimethyl butyric acid cyclopentyl ester (780mg, 1.69mmol) was dissolved in ethanol (40ml) and placed under a blanket of argon. 10% palladium on charcoal (80mg) was added and the mixture was stirred vigorously as hydrogen gas was bubbled through the system. After 30 minutes the suspension was placed under a balloon of hydrogen and stirred overnight at room temperature. The flask was purged with argon before removing the catalyst by filtration. The filtrate was concentrated under reduced pressure to provide the title compound as a white foam (458mg, 73%). ^{1}H-NMR; δ (CD_3OD, rotamers), 0.84 (0.4H, s), 7.82 (0.6H, s), 5.19-5.15 (1H, m), 4.27 (1H, s), 3.82-3.61 (1.4H, m), 3.45-3.37 (0.6H, m), 3.10-2.88 (1H, m), 1.89-1.31 (14H, m), 1.01 (3.6H, s), 0.99 (5.4H, s) and 0.92-0.87 (3H, m). ^{13}C-NMR; δ ($CDCl_3$ rotamers), 172.8, 171.1, 78.7, 78.4, 60.4, 60.2, 51.7, 48.0, 46.2, 44.8, 34.9, 34.7, 32.7, 32.6, 30.1,

29.9, 29.3, 29.2, 26.6, 23.6, 22.6 and 13.8. IR (refection disc) ν_{max} 2978, 1740, 1690, 1549, 1379, 1237, 1171, 984, 882 cm^{-1}. LRMS: 393 (M+Na), 369 (M-H).

The compounds of Examples 4-6 were preparedby the method of Example 3, by using the appropriate amino acid derivative instead of *tert*-leucine cyclopentyl ester in Step E:

Example 4

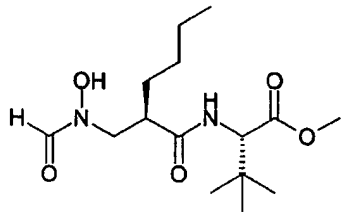
2S-{2R-[(Formyl-hydroxy-amino)-methyl]-hexanoylamino}-3-phenyl-propionic acid cyclo-pentyl ester



^{1}H-NMR; δ (CD_3OD rotamers), 8.13 (0.4H, s), 7.81 (0.6H, s), 7.36-6.92 (5H, m), 5.11-5.07 (1H, m), 4.61 (1H, t, J=7.6Hz), 3.65-3.46 (1H, m), 3.42-3.30 (1H, m), 3.19-2.92 (2H, m), 2.89-2.77 (0.6H, m), 2.74-2.51 (0.4H, m), 1.98-1.29 (14H, m) and 0.89-0.81 (3H, m). ^{13}C-NMR; δ (CD_3OD rotamers), 173.0, 171.6, 136.2, 129.8, 129.6, 129.1, 129.0, 127.7, 127.5, 79.6, 79.0, 53.9, 53.6, 51.9, 48.5, 46.4, 45.0, 38.6, 38.0, 33.0, 32.9, 30.3, 30.2, 29.6, 29.5, 24.0, 23.0 and 14.2. IR (reflection disc); ν_{max} 3325, 2958, 1731, 1663, 1532, 1443, 1367, 1280, 1199, 1104, 1079, 1032, 885, 749 and 699 cm-1. LRMS; +ve ion 427 (M+Na); -ve ion 403 (M-1).

Example 5

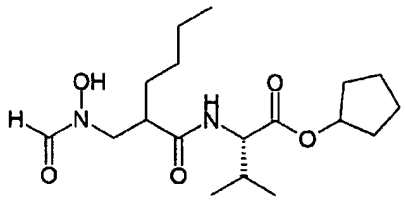
2S-{2R-[(Formyl-hydroxy-amino)-methyl]-hexanoylamino}-3,3-dimethyl butyric acid methyl ester



m.p. 63.5-64.5°C. ^{1}H-NMR; δ (CD_3OD, rotamers), 8.24 (0.3H, s), 7.82 (0.7H, s), 4.33 (1H, s), 3.82-3.58 (1.3H, m), 3.70 (3H, s), 3.45-3.37 (0.7H, m), 3.11-3.01 (0.7H, m), 2.95-2.83 (0.3H, m), 1.55-1.20 (6H, m), 1.00 (3H, s), 0.99 (6H, s) and 0.93-0.88 (3H, m). ^{13}C-NMR; δ (CD_3OD), 176.6, 173.2, 62.7, 53.9, 52.5, 45.4, 35.3, 31.6, 30.6, 27.6, 24.1 and 14.7. IR (refection disc); ν_{max} 3318, 2955, 1738, 1661, 1642, 1549, 1530, 1465, 1443, 1352, 1216, 1165, 1104, 1040, 1008 and 879 cm^{-1}. LRMS; +ve ion 339 (M+Na), -ve ion 315 (M-H).

Example 6

2S-{2R-[(Formyl-hydroxy-amino)-methyl]-hexanoylamino}-3-methyl butyric acid cyclo-pentyl ester

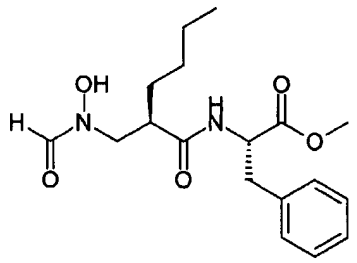


Pale yellow oil. ^{1}H-NMR; δ (CD_3OD, rotamers), 8.25 (0.4H, s), 7.82 (0.6H, s), 5.19-5.15 (1H, m), 4.24 (1H, d, J=6.3 Hz), 3.81-3.62 (1.4H, m), 3.49-3.38 (0.6H, m), 3.01-2.92 (0.6H, m), 2.81-2.75 (0.4H, m), 2.17-2.00 (1H, m), 1.90-1.34 (14H, m) and 0.95-0.88 (9H, m). ^{13}C-NMR; δ (CD_3OD), 176.6, 173.2, 159.8, 79.7, 60.0, 53.9, 45.8, 45.6, 34.0, 32.0, 31.5, 30.7, 25.0, 24.1, 19.9, 19.1 and 14.7. LRMS; +ve ion 379 (M+Na), -ve ion 355 (M-H).

The compounds of Example 7-10 were prepared by the method of Example 3 by parallel synthesis, using the appropriate amino acid derivative instead of *tert*-leucine cyclopentyl ester in Step E. The products were purified by preparative HPLC:

Example 7

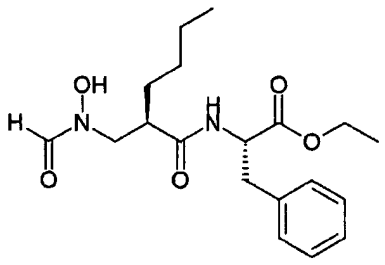
2S-{2R-[(Formyl-hydroxy-amino)-methyl]-hexanoylamino}-3-phenyl-propionic acid methyl ester



LRMS; +ve ion 373 (M+Na), -ve ion 349 (M-H).

Example 8

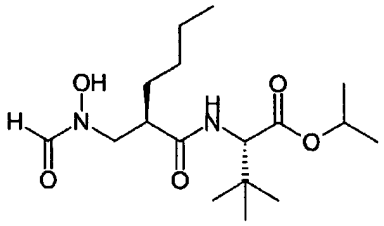
2S-{2R-[(Formyl-hydroxy-amino)-methyl]-hexanoylamino}-3-phenyl-propionic acid ethyl ester



LRMS; +ve ion 387 (M+Na), -ve ion 363 (M-H).

Example 9

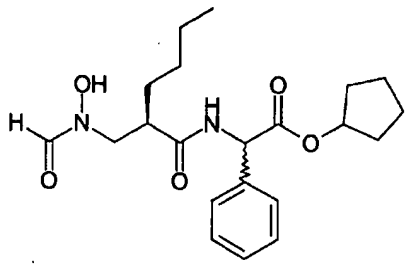
2S-{2R-[(Formyl-hydroxy-amino)-methyl]-hexanoylamino}-3,3-dimethyl butyric acid *iso*-propyl ester



LRMS; +ve ion 367 (M+Na), -ve ion 343 (M-H)

Example 10

2R (or S)-{2R-[(Formyl-hydroxy-amino)-methyl]-hexanoylamino}-2-phenyl acetic acid cyclpentyl ester

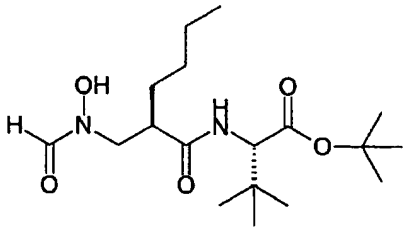


LRMS; +ve ion 413 (M+Na), 391 (M+H), -ve ion 389 (M-H)

Example 11 was prepared by the method of Example 3, by using the appropriate amino acid derivative instead of *tert*-leucine cyclopentyl ester in step E:

Example 11

2S-{2R-[(Formyl-hydroxy-amino)-methyl]-hexanoylamino}-3,3-dimethyl-butyric acid *tert*-butyl ester



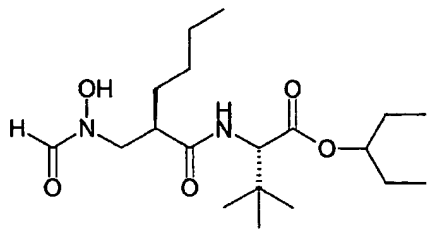
m.p. 76.1-78.2°C. ^{1}H-NMR; δ $CDCl_3$, rotamers), 8.37 (0.4H, s), 7.80 (0.6H, s), 6.42 (0.4H, d, J=9.3Hz), 6.29 (0.6H, d, J=9.5Hz), 4.33 (1H, d J=9.5Hz), 3.98 (0.4H, dd,

J=14.6, 7.3Hz), 3.85 (0.6H, dd, J=14.1, 9.6Hz), 3.64 (0.4H, dd, J=14.6, 3.5Hz), 3.45 (0.6H, dd, J=14.1, 4.2Hz), 2.85-2.75 (0.6H, m), 2.73-2.66 (0.4H, m), 1.67-1.19 (6H, m), 1.47 (9H, s), 0.99 (3H, s), 0.94 (6H, s) and 0.90-0.85 (3H, m). ^{13}C-NMR; δ ($CDCl_3$, rotamers) 176.3, 173.1, 170.9, 82.5, 61.2, 61.0, 52.1, 48.4, 46.7, 45.3, 35.0, 30.5, 30.4, 29.7, 29.6, 28.4, 27.0, 22.9 and 14.3. IR (reflection disc); ν_{max} 3405, 2967, 1708, 1680, 1653, 1524, 1474, 1369, 1285, 1238 and 1173 cm-1. LRMS; +ve ion 381 [M+Na], -ve ion 357 [M-1].

The compounds of Examples 12 and 13 were prepared by the method of Example 3 by parallel synthesis, using the appropriate amino acid derivative instead of *tert* leucine cyclopentyl ester in Step E. The products were purified by preparative HPLC:

Example 12

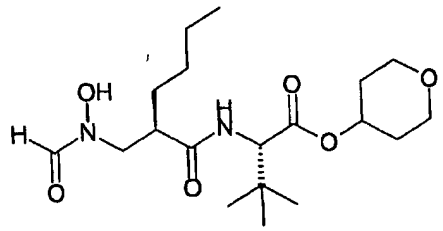
2S-{2R-[(Formyl-hydroxy-amino)-methyl]-hexanoylamino}-3,3-dimethyl-butyric acid 1-ethyl-propyl ester



LRMS; +ve ion 373 [M+1], 395 [M+Na], -ve ion 371 [M-1].

Example 13

2S-{2R-[(Formyl-hydroxy-amino)-methyl]-hexanoylamino}-3,3-dimethyl-butyric acid tetrahydro-pyran-4-yl ester

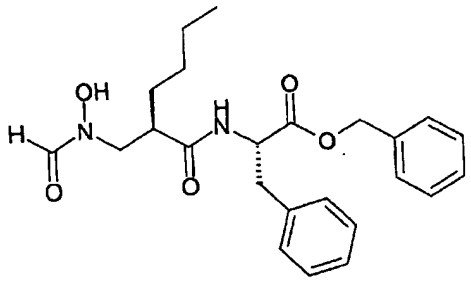


LRMS; +ve ion 387 [M+1], 409 [M+Na], -ve ion 385 [M-1].

The compounds of Examples 14 and 15 were prepared from 2R-(*tert*-butoxyamino-methyl)-hexanoic acid and the appropriate amino acid derivative by anology with methods described for Example 3:

Example 14

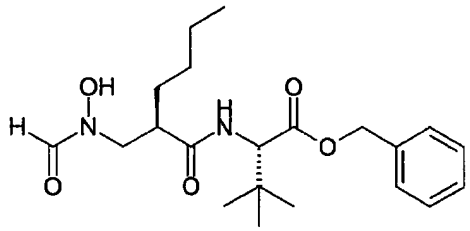
2S-{2R-[(Formyl-hydroxy-amino)-methyl]-hexanoylamino}-3-phenyl-propionic acid benzyl ester



^{1}H-NMR; δ $CDCl_3$, rotamers) 8.33 (0.4H, s), 7.79 (0.6H, s), 7.37-7.21 (8H, m), 7.01-6.98 (2H, m), 6.24-6.15 (1H, m), 5.21-5.07 (2H, m), 4.94-4.84 (1H, m), 3.91 (0.4H, dd, J=14.7, 7.4Hz), 3.77 (0.6H, dd, J=14.3, 9.7Hz), 3.55 (0.4H, dd, J=14.5, 3.4Hz), 3.43 (0.6H, dd, J=14.2, 4.4Hz), 3.25-2.98 (2H, m), 2.71-2.64 (0.6H, m), 2.52-2.51 (0.4H, m), 1.56-1.25 (6H, m) and 0.84 (3H,br.s). ^{13}C-NMR; δ ($CDCl_3$, rotamers) 157.7, 172.5, 171.2, 135.5, 135.3, 135.0, 134.8, 129.3, 129.2, 128.7, 128.6, 127.4, 127.2, 67.7, 67.4, 53.4, 50.8, 48.0, 46.1, 44.6, 38.0, 37.6, 29.9, 29.8, 29.1, 29.0, 22.5 and 13.7. LRMS; +ve ion 427 [M+1], 449 [M+Na].

Example 15

2S-{2R-[(Formyl-hydroxy-amino)-methyl]-hexanoylamino}-3,3-dimethyl-butyric acid benzyl ester

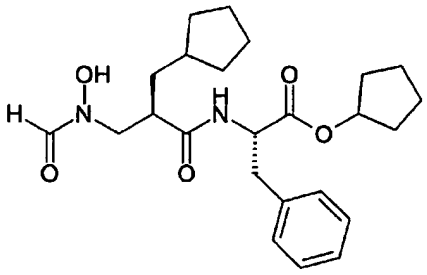


^{1}H-NMR; δ ($CDCl_3$, rotamers) 8.35 (0.2H, s), 7.74 (0.8H, s), 7.35 (5H, s), 6.50 (1H, d, J=9.3Hz), 5.21-5.15 (2H, m), 4.45 (1H, d, J=9.3Hz), 3.98 (0.2H, dd, J=14.6, 7.4Hz), 3.82 (0.8H, dd, J=14.1, 9.8Hz), 3.62 (0.2H, dd, J=14.7, 3.5Hz), 3.42 (0.8H, dd, J=14.1, 3.9Hz), 2.88-2.74 (0.8H, m), 2.71-2.63 (0.2H, m), 1.66-1.16 (6H, m), and 0.98-0.83 (12H, m). ^{13}C-NMR; δ ($CDCl_3$, rotamers)176.4, 173.4, 171.6, 135.6, 129.0, 128.9, 67.7, 67.4, 60.9, 60.7, 52.6, 48.3, 46.5, 45.0, 35.3, 35.1, 30.5, 30.3, 29.6, 29.5, 27.0, 26.9, 22.9 and 14.3. LRMS; +ve ion 393 [M+1], 415 [M+Na], -ve ion 391 [M-1].

Example 16 was prepared from 3-benzyloxyamino-2R-cyclopentylmethyl-propionic acid and phenylalanine cyclopentyl ester by analogy with methods described in patent number WO 99/39704:

Example 16

2S-[2R-Cyclopentylmethyl-3-(formyl-hydroxy-amino)-propionylamino]-3-phenyl-propionic acid cyclopentyl ester



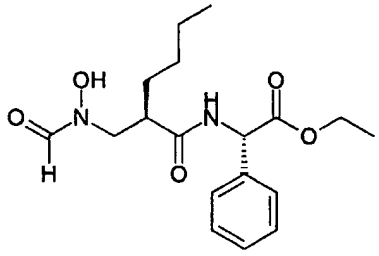
m.p. 76.8-78.5°C. ^{1}H-NMR; δ $CDCl_3$, rotamers) 8.34 (0.3H, s), 7.78 (0.7H, s), 7.34-7.09 (5H, m), 6.38-6.33 (1H, m), 5.24-5.19 (0.4H, m), 5.15-5.11 (0.6H, m), 4.83-4.71 (1H, m), 3.91(0.4H, dd, J=14.6, 7.4Hz), 3.76 (0.6H, dd, J=14.1, 9.5Hz), 3.55 (0.4H, dd, J=14.6, 3.4Hz), 3.42 (0.6H, dd, J=14.1, 4.3Hz), 3.23-2.92 (2H, m), 2.82-2.73 (0.7H, m), 2.58-2.56 (0.3H, m), 1.87-1.27 (17H, m) and 1.05-1.03 (2H, m). ^{13}C-NMR; δ ($CDCl_3$, rotamers) 176.0, 173.1, 171.7, 171.5, 136.2, 136.1, 129.8, 129.6, 129.1, 128.9, 127.7, 127.5, 79.6, 79.0, 53.9, 53.6, 52.4, 48.8, 45.7, 44.4, 38.6, 38.0, 37.9, 37.7, 36.9, 36.8, 33.4, 33.3, 33.0, 32.9, 32.8, 32.7, 25.6, 25.5 and 24.0. IR (reflection disc); V_{max} 3329, 2946, 2864, 1732, 1682, 1644, 1525, 1445, 1345, 1252, 1196 and 881 cm-1. LRMS; +ve ion 431 [M+1], -ve ion 429 [M-1].

Examples 17-28

Further compounds useful in accordance with the invention are those specifically named and characterised in International patent application WO 99/41232, as follows:

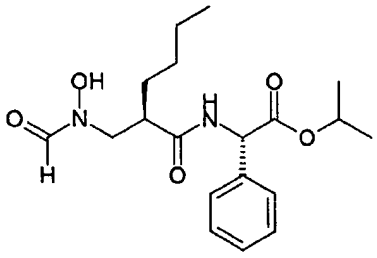
Example 17

2S-{2R-[(Formyl-hydroxy-amino)-methyl]-hexanoylamino}-2-phenyl acetic acid ethyl ester (Example 10 of WO 99/41232.)



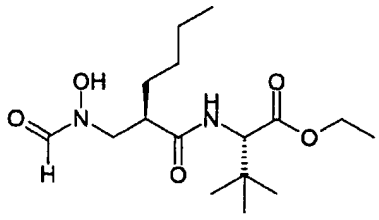
Example 18

S-{2R-[(Formyl-hydroxy-amino)-methyl]-hexanoylamino}-2-phenyl acetic acid *iso*-propyl ester (Example 11 of WO 99/41232.)



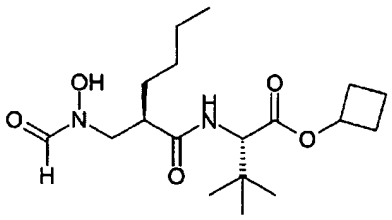
Example 19

2S-{2R-[(Formyl-hydroxy-amino)-methyl]-hexanoylamino}-3,3-dimethyl butyric acid ethyl ester (Example 12 of WO 99/41232.)



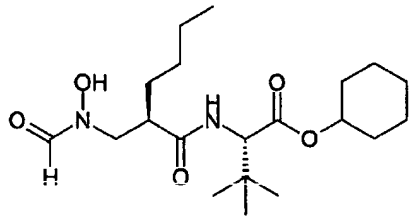
Example 20

2S-{2R-[(Formyl-hydroxy-amino)-methyl]-hexanoylamino}-3,3-dimethyl butyric acid cyclobutyl ester (Example 14 of WO 99/41232.)



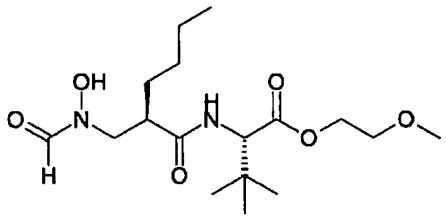
Example 21

2S-{2R-[(Formyl-hydroxy-amino)-methyl]-hexanoylamino}-3,3-dimethyl butyric acid cyclohexyl ester (Example 15 of WO 99/41232.)



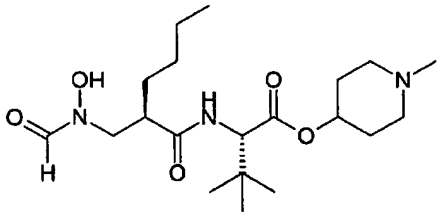
Example 22

2S-{2R-[(Formyl-hydroxy-amino)-methyl]-hexanoylamino}-3,3-dimethyl butyric acid 2-methoxy-ethyl ester (Example 16 of WO 99/41232.)



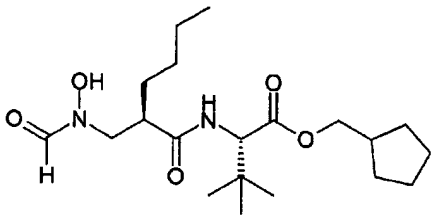
Example 23

2S-{2R-[(Formyl-hydroxy-amino)-methyl]-hexanoylamino}-3,3-dimethyl butyric acid 1-methyl-piperidin-4-yl ester (Example 17 of WO 99/41232.)



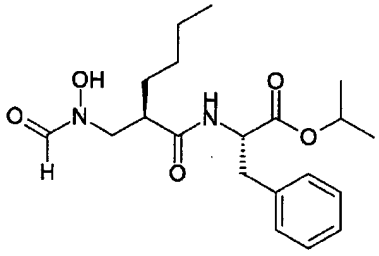
Example 24

2S-{2R-[(Formyl-hydroxy-amino)-methyl]-hexanoylamino}-3,3-dimethyl butyric acid cyclopentylmethyl ester (Example 18 of WO 99/41232.)



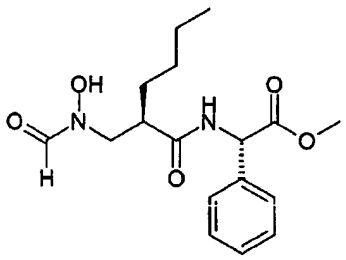
Example 25

2S-{2R-[(Formyl-hydroxy-amino)-methyl]-hexanoylamino}-3-phenyl-propionic acid *iso*-propyl ester (Example 19 of WO 99/41232.)



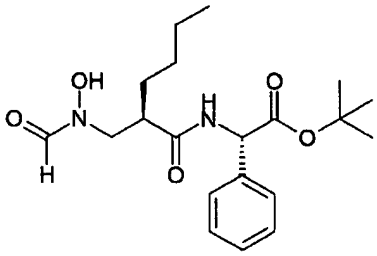
Example 26

S-{2R-[(Formyl-hydroxy-amino)-methyl]-hexanoylamino}-2-phenyl acetic acid methyl ester (Example 20 of WO 99/41232.)



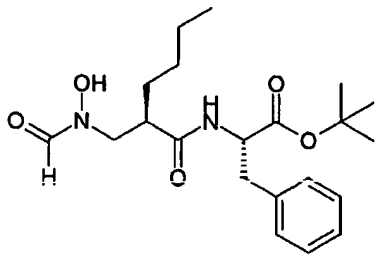
Example 27

S-{2R-[(Formyl-hydroxy-amino)-methyl]-hexanoylamino}-2-phenyl acetic acid *tert*-butyl ester (Example 21 of WO 99/41232.)



Example 28

2S-{2R-[(Formyl-hydroxy-amino)-methyl]-hexanoylamino}-3-phenyl-propionic acid *tert*- butyl ester (Example 22 of WO 99/41232.)



Biological Example

Inhibition of Leukotriene Synthesis by Rat Basophilic Leukaemia Cells

The rat basophilic leukaemia cell line RBL-1 was obtained from ATCC or ECACC and cultured in Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% foetal bovine serum, non-essential amino acids, sodium pyruvate, penicillin, streptomycin and 2mM glutamine, at 37°C in an atmosphere of 5% CO_2 in air, as recommended by the culture collection.

RBL-1 cells were harvested during log growth, washed and resuspended in Hanks Balanced Salt Solution, without calcium chloride and magnesium chloride, supplemented with 10% foetal bovine serum and penicillin, streptomycin, and 2mM glutamine and adjusted to a final cell concentration of $1.25X10^5$ cells/ml. Cells incubated in the presence of the appropriate concentration of inhibitor or vehicle for 4.75 hours at 37°C. Cells then transferred to ice for 15 minutes. Cells washed by centrifugation and resuspension in pre-chilled Phosphate Buffered Saline, with calcium chloride and magnesium chloride, supplemented with the appropriate concentration of test sample. After the PBS wash, cells resuspended at a final cell concentration of equalivent to $2.35X10^6$ cell/ml in PBS/sample buffer. Cells transferred to a microfuge tube on ice prior to ionophore stimulation.

Treated cells then exposed to 10μM A23187 for 15 minutes at 37°C . Cells

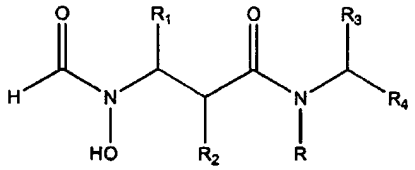
transferred to ice, thereby stopping the reaction. Cell free supernatant harvested by centrifugation. The levels of leukotriene B_4 then determined in the cell free supernatant using the Leukotriene B_4 [^{3}H] assay system from Amersham Pharmacia Biotech.

Using this methodology the IC_{50} value for the compound of example 4 was estimated as 0.7nM and for Kelatorphan as 350nM.

Claims

Claims

1. A method of treatment of mammals suffering diseases responsive to inhibition of intracellular leukotriene-A_4 hydrolase activity, comprising administering to the mammal suffering such disease an amount of a compound of general formula (I) or a pharmaceutically acceptable salt hydrate or solvate thereof sufficient to inhibit such activity:

(I) 

wherein

R is hydrogen or (C_1-C_6)alkyl;

R_1 is hydrogen;

(C_1-C_6)alkyl;

(C_2-C_6)alkenyl;

phenyl or substituted phenyl;

phenyl (C_1-C_6)alkyl or substituted phenyl(C_1-C_6)alkyl;

phenyl (C_2-C_6)alkenyl or substituted phenyl(C_2-C_6)alkenyl

heterocyclyl or substituted heterocyclyl;

heterocyclyl(C_1-C_6)alkyl or substituted heterocyclyl(C_1-C_6)alkyl;

a group BSO_nA- wherein n is 0, 1 or 2 and B is hydrogen or a (C_1-C_6) alkyl, phenyl, substituted phenyl, heterocyclyl substituted heterocyclyl, (C_1-C_6)acyl, phenacyl or substituted phenacyl group, and A represents (C_1-C_6)alkylene;

amino(C_1-C_6)alkyl, (C_1-C_6)alkylamino(C_1-C_6)alkyl, di(C_1-C_6)alkylamino(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, mercapto(C_1-C_6)alkyl or carboxy(C_1-C_6) alkyl wherein the amino-, hydroxy-, mercapto- or carboxyl-group are optionally protected or the carboxyl- group amidated;

lower alkyl substituted by carbamoyl, mono(lower alkyl)carbamoyl, di(lower alkyl)carbamoyl, di(lower alkyl)amino, or carboxy-lower alkanoylamino; or

a cycloalkyl, cycloalkenyl or non-aromatic heterocyclic ring containing up to 3 heteroatoms, any of which may be (i) substituted by one or more substituents selected from C_1-C_6 alkyl, C_2-C_6 alkenyl, halo, cyano (-CN), $-CO_2H$, $-CO_2R$, $-CONH_2$, -CONHR, $-CON(R)_2$, -OH, -OR, oxo-, -SH, -SR, -NHCOR, and $-NHCO_2R$ wherein R is C_1-C_6 alkyl or benzyl and/or (ii) fused to a cycloalkyl or heterocyclic ring;

R_2 is a C_1-C_{12} alkyl,
C_2-C_{12} alkenyl,
C_2-C_{12} alkynyl,
phenyl(C_1-C_6 alkyl)-,
heteroaryl(C_1-C_6 alkyl)-,
phenyl(C_2-C_6 alkenyl)-,
heteroaryl(C_2-C_6 alkenyl)-,
phenyl(C_2-C_6 alkynyl)-,
heteroaryl(C_2-C_6 alkynyl)-,
cycloalkyl(C_1-C_6 alkyl)-,

cycloalkyl(C_2-C_6 alkenyl)-,
cycloalkyl(C_2-C_6 alkynyl)-,
cycloalkenyl(C_1-C_6 alkyl)-,
cycloalkenyl(C_2-C_6 alkenyl)-,
cycloalkenyl(C_2-C_6 alkynyl)-,
phenyl(C_1-C_6 alkyl)O(C_1-C_6 alkyl)-, or
heteroaryl(C_1-C_6 alkyl)O(C_1-C_6 alkyl)- group,
any one of which may be optionally substituted by
C_1-C_6 alkyl,
C_1-C_6 alkoxy,
halo,
cyano (-CN),
phenyl or heteroaryl, or
phenyl or heteroaryl substituted by
C_1-C_6 alkyl,
C_1-C_6 alkoxy,
halo, or
cyano (-CN);

R_3 is the characterising group of a natural or non-natural α amino acid in which any functional groups may be protected; and

R_4 is an ester or thioester group.

2. The use of a compound of formula (I) as defined in claim 1 in the preparation of a composition for treatment of mammals suffering diseases responsive to inhibition of intracellular leukotriene-A_4 hydrolase activity.

3. A method as claimed in claim 1 or the use as claimed in claim 2 wherein the stereochemical configuration of the carbon atom carrying the groups R_3 and R_4 is S.

4. A method as claimed in claim 1, the use or claim 2, or a method or use as claimed in claim 3, wherein R_1 is:

hydrogen, methyl, ethyl, n-propyl, n-butyl, isobutyl, cyclopropylmethyl, allyl, phenylpropyl, phenylprop-2-enyl, thienylsulphanylmethyl, thienylsulphinylmethyl, or thienylsulphonylmethyl; or

C_1-C_4 alkyl,eg methyl, ethyl n-propyl or n-butyl, substituted by a phthalimido, 1,2-dimethyl-3,5-dioxo-1,2,4-triazolidin-4-yl, 3-methyl-2,5-dioxo-1-imidazolidinyl, 3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl, 2-methyl-3,5-dioxo-1,2,4-oxadiazol-4-yl, 3-methyl-2,4,5-trioxo-1-imidazolidinyl, 2,5-dioxo-3-phenyl-1-imidazolidinyl, 2-oxo-1-pyrrolidinyl, 2,5-dioxo-1-pyrrolidinyl or 2,6-dioxopiperidinyl, 5,5-dimethyl-2,4-dioxo-3-oxazolidinyl, hexahydro-1,3-dioxopyrazolo[1,2,a][1,2,4]-triazol-2-yl, or a naphththalimido (ie 1,3-dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl), 1,3-dihydro-1-oxo-2H-benz[f]isoindol-2-yl, 1,3-dihydro-1,3-dioxo-2H-pyrrolo[3,4-b]quinolin-2-yl, or 2,3-dihydro-1,3-dioxo-1H-benz[d,e]isoquinolin-2-yl group; or

cyclohexyl, cyclooctyl, cycloheptyl, cyclopentyl, cyclobutyl, cyclopropyl, tetrahydropyranyl or morpholinyl.

5. A method as claimed in claim 1, the use or claim 2, or a method or use as claimed in claim 3, wherein R_1 is hydrogen, cyclopropylmethyl, n-propyl, or allyl.

6. A method as claimed in claim 1, the use or claim 2, or a method or use as claimed in claim 3, wherein R_2 is:

C_1-C_{12} alkyl, C_3-C_6 alkenyl or C_3-C_6 alkynyl;

phenyl(C_1-C_6 alkyl)-, phenyl(C_3-C_6 alkenyl)- or phenyl(C_3-C_6 alkynyl)- optionally substituted in the phenyl ring;

heteroaryl(C_1-C_6 alkyl)-, heteroaryl(C_3-C_6 alkenyl)- or heteroaryl(C_3-C_6 alkynyl)- optionally substituted in the heteroaryl ring;

4-phenylphenyl(C_1-C_6 alkyl)-, 4-phenylphenyl(C_3-C_6 alkenyl)-, 4-phenylphenyl(C_3-C_6 alkynyl)- , 4-heteroarylphenyl(C_1-C_6 alkyl)-, 4-heteroarylphenyl(C_3-C_6 alkenyl)-, 4-heteroarylphenyl(C_3-C_6 alkynyl)-, optionally substituted in the terminal phenyl or heteroaryl ring; or

phenoxy(C_1-C_6 alkyl)- or heteroaryloxy(C_1-C_6 alkyl)- optionally substituted in the phenyl or heteroaryl ring.

7. A method as claimed in claim 1, the use or claim 2, or a method or use as claimed in claim 3, wherein R_2 is: methyl, ethyl, n- or iso-propyl, n- , iso- or tert-butyl, n-pentyl, n-hexyl, n-heptyl, n-nonyl, n-decyl, prop-2-yn-1-yl, 3-phenylprop-2-yn-1-yl, 3-(2-chlorophenyl)prop-2-yn-1-yl, benzyl phenylpropyl, 4-chlorophenylpropyl, 4-methylphenylpropyl, 4-methoxyphenylpropyl, phenoxybutyl, 3-(4-pyridylphenyl)propyl-, 3-(4-(4-pyridyl)phenyl)prop-2-yn-1-yl, 3-(4-phenylphenyl)propyl-, 3-(4-phenyl)phenyl)prop-2-yn-1-yl or 3-[(4-chlorophenyl)phenyl]propyl-.

8. A method as claimed in claim 1, the use or claim 2, or a method or use as claimed in claim 3, wherein R_2 is benzyl, n-butyl, iso-butyl, n-hexyl, or cyclopentylmethyl.

9. A method as claimed in claim 1, the use or claim 2, or a method or use as claimed in claim 3, wherein R_3 is C_1-C_6 alkyl, phenyl, 2,- 3-, or 4-pyridyl, 2- or 3-thienyl, 2,- 3-, or 4-hydroxyphenyl, 2,- 3-, or 4-methoxyphenyl, 2,- 3-, or 4-pyridylmethyl, benzyl, 2,- 3-, or 4-hydroxybenzyl, 2,- 3-, or 4-benzyloxybenzyl, 2,- 3-, or 4-C_1-C_6 alkoxybenzyl, or benzyloxy(C_1-C_6alkyl)-.

10. A method as claimed in claim 1, the use or claim 2, or a method or use as

claimed in claim 3, wherein R_3 is the characterising group of a natural α amino acid, in which any functional group may be protected, any amino group may be acylated and any carboxyl group present may be amidated.

11. A method as claimed in claim 1, the use or claim 2, or a method or use as claimed in claim 3, wherein R_3 is a group $-[Alk]_nR_8$ where Alk is a (C_1-C_6)alkyl or (C_2-C_6)alkenyl group optionally interrupted by one or more -O-, or -S- atoms or $-N(R_7)-$ groups [where R_7 is a hydrogen atom or a (C_1-C_6)alkyl group], n is 0 or 1, and R_8 is an optionally substituted cycloalkyl or cycloalkenyl group.

12. A method as claimed in claim 1, the use or claim 2, or a method or use as claimed in claim 3, wherein R_3 is a benzyl group substituted in the phenyl ring by a group of formula $-OCH_2COR_8$ where R_8 is hydroxyl, amino, (C_1-C_6)alkoxy, phenyl(C_1-C_6)alkoxy, (C_1-C_6)alkylamino, di$((C_1-C_6)$alkyl)amino, phenyl(C_1-C_6)alkylamino, the residue of an amino acid or acid halide, ester or amide derivative thereof, said residue being linked via an amide bond, said amino acid being selected from glycine, α or β alanine, valine, leucine, isoleucine, phenylalanine, tyrosine, tryptophan, serine, threonine, cysteine, methionine, asparagine, glutamine, lysine, histidine, arginine, glutamic acid, and aspartic acid.

13. A method as claimed in claim 1, the use or claim 2, or a method or use as claimed in claim 3, wherein R_3 is a heterocyclic(C_1-C_6)alkyl group, either being unsubstituted or mono- or di-substituted in the heterocyclic ring with halo, nitro, carboxy, (C_1-C_6)alkoxy, cyano, (C_1-C_6)alkanoyl, trifluoromethyl (C_1-C_6)alkyl, hydroxy, formyl, amino, (C_1-C_6)alkylamino, di-(C_1-C_6)alkylamino, mercapto, (C_1-C_6)alkylthio, hydroxy(C_1-C_6)alkyl, mercapto(C_1-C_6)alkyl or (C_1-C_6)alkylphenylmethyl.

14. A method as claimed in claim 1, the use or claim 2, or a method or use as claimed in claim 3, wherein R_3 is a group $-CR_aR_bR_c$ in which:

each of R_a, R_b and R_c is independently hydrogen, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, phenyl(C_1-C_6)alkyl, (C_3-C_8)cycloalkyl; or

R_c is hydrogen and R_a and R_b are independently phenyl or heteroaryl such as pyridyl; or

R_c is hydrogen, $(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, phenyl$(C_1$-$C_6)$alkyl, or $(C_3$-$C_8)$cycloalkyl, and R_a and R_b together with the carbon atom to which they are attached form a 3 to 8 membered cycloalkyl or a 5- to 6-membered heterocyclic ring; or

R_a, R_b and R_c together with the carbon atom to which they are attached form a tricyclic ring (for example adamantyl); or

R_a and R_b are each independently $(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, phenyl$(C_1$-$C_6)$alkyl, or a group as defined for R_c below other than hydrogen, or R_a and R_b together with the carbon atom to which they are attached form a cycloalkyl or heterocyclic ring, and R_c is hydrogen, -OH, -SH, halogen, -CN, -CO_2H, $(C_1$-$C_4)$perfluoroalkyl, -CH_2OH, -$CO_2(C_1$-$C_6)$alkyl, -O$(C_1$-$C_6)$alkyl, -O$(C_2$-$C_6)$alkenyl, -S$(C_1$-$C_6)$alkyl, -SO$(C_1$-$C_6)$alkyl, -$SO_2(C_1$-$C_6)$ alkyl, -S$(C_2$-$C_6)$alkenyl, -SO$(C_2$-$C_6)$alkenyl, -$SO_2(C_2$-$C_6)$alkenyl or a group -Q-W wherein Q represents a bond or -O-, -S-, -SO- or -SO_2- and W represents a phenyl, phenylalkyl, $(C_3$-$C_8)$cycloalkyl, $(C_3$-$C_8)$cycloalkylalkyl, $(C_4$-$C_8)$cycloalkenyl, $(C_4$-$C_8)$cycloalkenylalkyl, heteroaryl or heteroarylalkyl group, which group W may optionally be substituted by one or more substituents independently selected from, hydroxyl, halogen, -CN, -CO_2H, -$CO_2(C_1$-$C_6)$alkyl, -$CONH_2$, -CONH$(C_1$-$C_6)$alkyl, -CONH$(C_1$-C_6alkyl$)_2$, -CHO, -CH_2OH, $(C_1$-$C_4)$perfluoroalkyl, -O$(C_1$-$C_6)$alkyl, -S$(C_1$-$C_6)$alkyl, -SO$(C_1$-$C_6)$alkyl, -$SO_2(C_1$-$C_6)$alkyl, -NO_2, -NH_2, -NH$(C_1$-$C_6)$alkyl, -N$((C_1$-$C_6)$alkyl$)_2$, -NHCO$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, $(C_3$-$C_8)$cycloalkyl, $(C_4$-$C_8)$cycloalkenyl, phenyl or benzyl.

15. A method as claimed in claim 1, the use or claim 2, or a method or use as claimed in claim 3, wherein R_3 is phenyl, benzyl, tert-butoxymethyl, iso-propyl or iso-butyl.

16. A method as claimed in claim 1, the use or claim 2, or a method or use as claimed in claim 3, wherein R_4 is a group of formula -(C=O)OR_9 , -(C=O)SR_9 , -(C=S)SR_9, and -(C=S)OR_9 wherein R_9 is (C_1-C_6)alkyl, (C_2-C_6)alkenyl, cycloalkyl, cycloalkyl(C_1-C_6)alkyl-, phenyl, heterocyclyl, phenyl(C_1-C_6)alkyl-, heterocyclyl(C_1-C_6)alkyl-, (C_1-C_6)alkoxy(C_1-C_6)alkyl-, or (C_1-C_6)alkoxy(C_1-C_6)alkoxy(C_1-C_6)alkyl-, any of which may be substituted on a ring or non-ring carbon atom or on a ring heteroatom, if present.

17. A method as claimed in claim 1, the use or claim 2, or a method or use as claimed in claim 3, wherein R_4 is a group of formula -(C=O)OR_9 wherein R_9 is methyl, ethyl, n-or iso-propyl, n-, sec- or tert-butyl, 1-ethyl-prop-1-yl, 1-methyl-prop-1-yl, 1-methyl-but-1-yl, cyclopentyl, cyclohexyl, allyl, phenyl, benzyl, 2-, 3- and 4-pyridylmethyl, N-methylpiperidin-4-yl, 1-methylcyclopent-1yl, adamantyl, tetrahydrofuran-3-yl or methoxyethyl.

18. A method as claimed in claim 1, the use or claim 2, or a method or use as claimed in claim 3, wherein R_4 is a group of formula -(C=O)OR_9 wherein R_9 is benzyl, cyclopentyl, cyclohexyl or isopropyl.

19. A method as claimed in claim 1, the use or claim 2, or a method or use as claimed in claim 3, wherein R is hydrogen or methyl.

20. A method as claimed in claim 1, the use or claim 2, or a method or use as claimed in claim 3, wherein R is hydrogen; R_1 is hydrogen, cyclopropylmethyl, n-propyl or allyl; R_2 is benzyl, n-butyl, iso-butyl, n-hexyl or cyclopentylmethyl; R_3 is phenyl, benzyl, tert-butoxymethyl, isopropyl or iso-butyl; and R_4 is a group of formula -(C=O)OR_9 wherein R_9 is benzyl, cyclopentyl, cyclohexyl or isopropyl.

21. A method as claimed in claim 1, the use or claim 2, or a method or use as claimed in any of claims 3-20, wherein the disease is asthma, rheumatoid arthritis,

osteoarthritis, multiple sclerosis, ulcerative colitis, contact or atopic dermatitis, psoriasis, inflammatory bowel disease or Crohn's disease.

INTERNATIONAL SEARCH REPORT

Int. ..tional Application No
PCT/GB 00/00162

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/216 A61K31/223 A61K31/351 A61K31/445 A61K31/16 A61P29/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,Y	WO 99 41232 A (BRITISH BIOTECH PHARM ;AYSCOUGH ANDREW PAUL (GB); DRUMMOND ALAN HA) 19 August 1999 (1999-08-19) cited in the application the whole document	1-21
P,Y	WO 99 40910 A (BRITISH BIOTECH PHARM ;WHITTAKER MARK (GB); AYSCOUGH ANDREW PAUL () 19 August 1999 (1999-08-19) the whole document	1-21
A	EP 0 082 088 A (ROQUES BERNARD ;SCHWARTZ JEAN CHARLES (FR); LECOMTE JEANNE MARIE () 22 June 1983 (1983-06-22) abstract; examples 48,77 page 79, line 7 -page 84, line 15; claims	1-21

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 May 2000	23/05/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Hoff, P

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INTERNATIONAL SEARCH REPORT

Int. tional Application No
PCT/GB 00/00162

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	FOURNIE-ZALUSKI M -C ET AL: "NEW BIDENTASES AS FULL INHIBITORS OF ENKEPHALIN-DEGRADING ENZYMES: SYNTHESIS AND ANALGESIS PROPERTIES" JOURNAL OF MEDICINAL CHEMISTRY,US,AMERICAN CHEMICAL SOCIETY. WASHINGTON, vol. 28, no. 9, 1 January 1985 (1985-01-01), pages 1158-1169, XP002019770 ISSN: 0022-2623 abstract; figure 3; table I	1-21
A	WO 94 10990 A (GALLOWAY WILLIAM ALAN ;BRITISH BIO TECHNOLOGY (GB); CRIMMIN MICHAE) 26 May 1994 (1994-05-26) abstract page 9, last paragraph page 14, paragraph 1 - paragraph 2; claims 3,20,21	1-21
A	WO 95 22966 A (SANOFI WINTHROP INC) 31 August 1995 (1995-08-31) cited in the application abstract; claims 1,9	1-21
A	WO 95 19965 A (GLYCOMED INC) 27 July 1995 (1995-07-27) cited in the application abstract page 27, line 3 -page 30, line 31; claims 1,2,10	1-21
A	PENNING ET AL: "Kelatorphan and related analogs: potent and selective inhibitors of leukotriene A4 hydrolase" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS,GB,OXFORD, vol. 5, no. 21, 1995, pages 2517-2522, XP002103716 ISSN: 0960-894X cited in the application the whole document	1-21

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 00/00162

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 1, 3-21
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 1, 3-21 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. ional Application No
PCT/GB 00/00162

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9941232 A	19-08-1999	AU 2534799 A	30-08-1999
WO 9940910 A	19-08-1999	AU 2432199 A	30-08-1999
EP 0082088 A	22-06-1983	FR 2518088 A	17-06-1983
		AT 18902 T	15-04-1986
		DE 3270317 D	07-05-1986
		JP 1679823 C	13-07-1992
		JP 3046463 B	16-07-1991
		JP 58150547 A	07-09-1983
		US 4618708 A	21-10-1986
		US 4738803 A	19-04-1988
WO 9410990 A	26-05-1994	AT 150300 T	15-04-1997
		AU 5430194 A	08-06-1994
		DE 69309094 D	24-04-1997
		DE 69309094 T	31-07-1997
		EP 0667770 A	23-08-1995
		ES 2101358 T	01-07-1997
		JP 8505605 T	18-06-1996
		US 5691382 A	25-11-1997
WO 9522966 A	31-08-1995	US 5514716 A	07-05-1996
		AU 1881795 A	11-09-1995
		CA 2184093 A	31-08-1995
		EP 0749302 A	27-12-1996
		FI 963298 A	23-10-1996
		HU 75054 A	28-03-1997
		JP 9509662 T	30-09-1997
		NO 963499 A	14-10-1996
		NZ 281856 A	19-12-1997
		US 5618844 A	08-04-1997
WO 9519965 A	27-07-1995	US 5892112 A	06-04-1999
		AU 1000399 A	04-03-1999
		AU 1604995 A	08-08-1995
		CA 2158760 A	27-07-1995
		EP 0690841 A	10-01-1996
		JP 9501183 T	04-02-1997
		US 5773438 A	30-06-1998